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13. ABSTRACT *(Maximum 200 words)*

During year one of this project, Cancer and Leukemia Group B (CALGB) wrote the extensive self-administered questionnaire comprising an essential element of protocol 9484 and circulated the protocol to its member institutions. At sixteen institutions the necessary Investigational Review Board (IRB) approval has been granted. Approval at the majority of the remaining 188 is anticipated shortly. After extensive pilot testing of early drafts of the questionnaires on healthy women and breast cancer patients, the telephone interview questionnaire has been perfected, the telephone interviewer hired and trained, an "800" number established, and the necessary pathways for the correlation of the phone interview information with clinical and laboratory data have been developed. The DNA extractor has been purchased, installed and tested, and the flow of patient samples from CALGB 9484 has started. Although it has taken longer than anticipated to reach a consensus and appropriate methodologies to resolve the ethical issues arising from studies of heritable cancer genes, the thorough approach taken during the current year will yield more rapid progress in year two of the project.

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N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

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N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

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Progress Report
Contract DAMD 17-94-J- 4114 from U.S. Army Research and Materiel Command

October 1, 1994-September 30, 1995
Prepared by O. Ross McIntrye, M.D. Principal Investigator

I. INTRODUCTION:

A. Nature of the problem:

The use of adjuvant chemotherapy following local treatment of the tumor has clearly benefited many patients with breast cancer[1]. On the other hand, adjuvant chemotherapy carries with it a number of potential risks including secondary malignancies. Thus, it would be desirable to give adjuvant therapy only to the subgroup of women with breast cancer who are most likely to have a recurrence. Although clinical findings are useful in assigning prognosis [2,3], these alone are imperfect measures and there is hope that additional tests, for instance the detection of certain somatic mutations in the tumor, will prove helpful in guiding the decision as to who should and who should not receive adjuvant chemotherapy. These considerations have now been formalized in the language describing such testing and a distinction between prognostic factors (which forecast clinical outcome) and predictive factors (which predict response and influence selection to specific forms of therapy) has been offered.[4]

In addition to our ability to detect a number of somatic mutations that may predict the risk of recurrence, it is now possible to identify those individuals who carry the BRCA 1 gene in their germline[5,6,7,8]. It is anticipated that soon additional genes conferring an increased risk of breast cancer upon their carriers will be identified. The presence or absence of such genes in the germline may influence not only risk of occurrence but also the response to treatment and other outcomes in these patients. Knowledge that such genes are present may predict for the likelihood of a second primary in women who have already been diagnosed with breast cancer, and may assist in guiding prevention efforts in other members of the family who carry the gene.

The investigators who are participating in this project will test a number of hypotheses that were described in our original application. In addition to these, new research proposals have been received by the steering committee. These include the following:

1. Evaluation of proliferation markers: Immunohistochemical expression of Ki-67 (MIB-1) and PCNA compared to SPF by flow cytometry. Proposed by Timothy Kute, Ph.D., Bowman Gray School of Medicine. This investigation proposes to use tissue already collected using other support but would be extended to tissue collected with support from this project, if preliminary studies are promising.

2. 06-Methylguanine-DNA Methyltransferase in breast cancer specimens from patients on 8782. Proposed by Marc Citron, M.D. Long Island Jewish Hospital.

3. African American breast cancer human genome study. An investigation of genomic DNA from African Americans proposed by the CALGB Minority Consortium, Dr. Diana Lake Chair, and Dr. Micheal Dean, NCI Frederick Cancer Research Center.

Because interactions of erb-2 and p53 with type of adjuvant therapy received have already been observed (see next section), it is important that assays of putative prognostic factors be performed on well-characterized groups of patients receiving adjuvant chemotherapy according to standardized protocols. The registry being created with support from this grant is quite different from usual population-based registry concepts. Instead, it may be viewed as a library in which clinical information on groups of uniformly staged and treated patients is located within a structure that also contains patient personal, family, and environmental exposure history, specimens from patients, and data from molecular and other laboratory studies. In contrast to a population-based registry, it offers an internally cohesive group of patients with well-defined disease, treatment and follow-up. It is possible to draw scientifically valid conclusions from this group by looking for interactions between treatment and factors such as genomic susceptibility and acquired somatic alterations.[9]

In cohorts of patients treated on our protocols endpoints such as time to recurrence, site of first recurrence, percentage of planned adjuvant therapy received, and detailed initial staging information are available. Moreover, there is an opportunity to collect additional information from such patients that may be useful in predicting the likelihood of a germline mutation or other factors that may interact with treatment and prognosis.

The identification in a patient or family member of a breast cancer patient of a heritable gene conferring an increased risk of breast cancer carries with it economic and psychosocial risks[10] in addition to the possibility that the gene is not causally related to the cancer in that patient[11]. We will be able to assess the impact of determining genomic susceptibility on individuals *most in need* of this type of information. The creation of the linked registry supported by this grant offers the opportunity for the patients and those involved in the laboratory to be joined in the pursuit of new knowledge. It is important that this pursuit be conducted in a manner offering the least psychological stress and the greatest protection from adverse social and economic consequences to those who participate. Collection of detailed information at the time of entry to the study relating to this as well as other areas will allow hypotheses concerning this aspect of the study to be tested.

B. Background and Previous Work

In order to show the value of our linked-registry we offer the example that follows. We emphasize that this is an early example of the type of success we hope to

achieve. The work that produced these results followed the successful integration of effort by a number of individuals, funded by a variety of sources including NCI grants to the CALGB, R01 and SPORE grants held by certain of the investigators, and by a small foundation grant to the CALGB.

Example: In 1989, the CALGB activated protocol 8869 with Hyman Muss, M.D., Bowman Gray School of Medicine, as study chair. The goal of this study was to pursue possible relationships between S phase and ploidy in breast cancer specimens as determined by flow cytometry techniques with clinical outcome in patients treated on our adjuvant protocol 8541. The protocol provided for collection of fixed tissue on a random sample of patients entered on the treatment study. As 8869 progressed, and as techniques were perfected for the immunohistochemical determination of erbB-2 and P53 on paraffin embedded specimens, the protocol was amended so that Ann Thor, M.D., Massachusetts General Hospital, could apply these tests to the specimens. In addition, molecular assessment of these tissues by Edison Liu, M.D., University of North Carolina was added at that time.

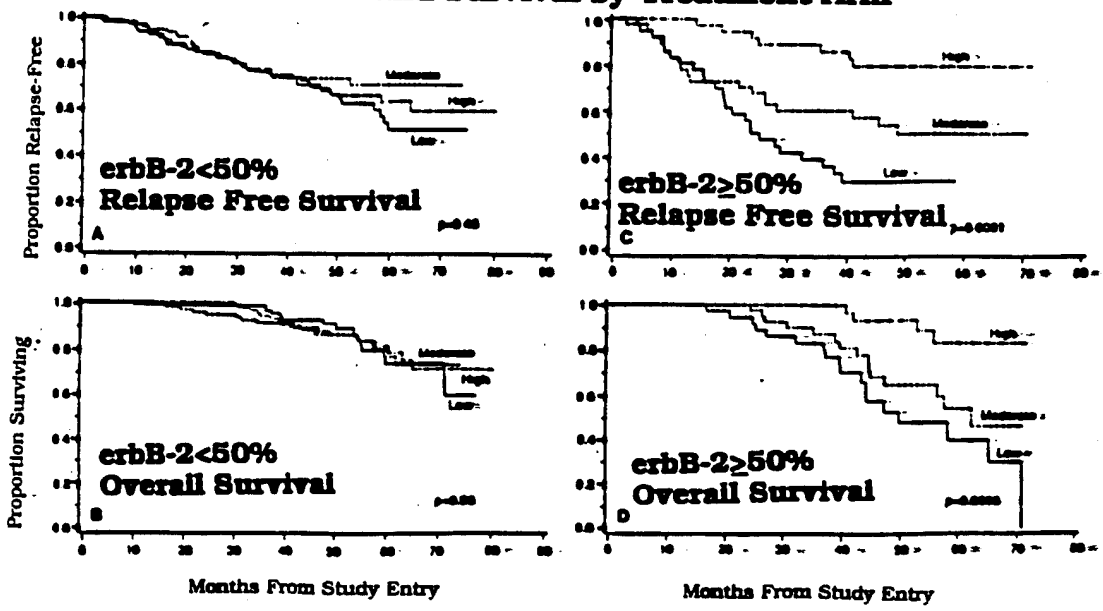
The treatment protocol, 8541, tested three CAF (cyclophosphamide, doxorubicin, and 5 fluorouracil) adjuvant regimens for which the dose schedule and dose intensity is shown in Table 1. Patients receiving the more dose intense regimens had significantly longer disease free and overall survival than patients receiving the lower dose regimen.[12, 13]

Table 1
Dose and Dose-Rates

Arm	I	II	III
Dose Rate mg/M2/week			
Cyclophosphamide	150	100	75
Doxorubicin	15	10	7.5
5-Fluorouracil	300	200	150
Cumulative Dose mg/M2			
Cyclophosphamide	2400	2400	1200
Doxorubicin	240	240	120
5-Fluorouracil	4800	4800	2400

When these treatment results are combined with studies of S-phase, P53 and erbB-2, an unexpected highly significant finding emerged.[14,15] The effect was most dramatic for erbB-2 which is shown in Figure 1, although similar results occurred when P53 overexpression[16,17] or S-phase was analyzed.

Figure 1
erbB-2 and Survival by Treatment Arm



As shown, the patients whose tumors overexpressed erbB-2 had a significantly longer disease-free and overall survival than those whose tumors did not overexpress erbB-2. There was no significant difference in disease free or overall survival with any of the three treatments for those patients whose tumors did not overexpress erbB-2. These findings indicate that the benefit of intensive adjuvant therapy with this combination is limited to a subgroup of patients. From the clinical data we know that the group receiving the more intensive treatments fared better, but without the integrated laboratory data, of course, we have no indication that this intensive treatment group was comprised of two populations, one which did, and the other which did not, respond to the more intensive treatments.

As stated above, 8869 originally collected specimens on a randomly selected sample of all patients on 8541. Committing almost all of the very limited non-NCI funds available to the CALGB, we immediately set about to collect all of the remaining slides available from patients on this study. These will allow a second set of determinations of S phase, P53 and erbB-2 that will be coupled with the clinical data in order to determine whether the above observations are confirmed. If they are, the implications for therapy using this common adjuvant program will be profound. For instance, it would be inappropriate to continue administering either of the two higher dose programs to women with low erbB-2 expression because of the risk of

increased toxicity. Instead we would mount a study to determine whether, for such patients, low dose CAF was different than no adjuvant treatment, and to test other adjuvant regimens in these patients.

In addition, the CALGB is investigating whether the effect of erbB-2 overexpression we observed is related to dose intensity of non-doxorubicin containing adjuvant regimens and we are testing the hypothesis that the doxorubicin dose intensity in the CAF regimen we used interacts with topoisomerase levels as influenced by erbB-2 overexpression.

Conclusion from the Example: This relationship between dose intensity, time to failure or death, and erbB-2 (or P53) overexpression would not have been easily discovered if the laboratory study had not been conducted on tissue samples of similarly staged patients receiving randomly assigned, defined therapeutic regimens.

Current status of our work: Subsequent to the presentation of this work in abstract form, the CALGB has had a large number of requests from its own members and from scientists outside the Group for access to additional sections from these tissue blocks. The Group set up a process for the review and consideration of these requests, but because of the limited number of tissue sections taken from the blocks prior to their return to the submitting institution and due to the limited resources available (which preclude obtaining the blocks for a second time) we have been able to make a suitable number of sections available to only one additional laboratory.

Also during this interval, a number of improvements in methodology occurred, especially the application of PCR techniques to DNA obtained from paraffin embedded sections, which allowed the extension of these methods to a large number of molecules of interest.

The rapidly building capabilities for this type of study and the excitement attending the initial success of combining laboratory and clinical information on our patients has led to several meetings of investigators. At these meetings there has been vigorous discussion of the opportunities for new projects as well as the need to develop new resources to serve CALGB as well as other investigators. The infrastructure category of the Army BAA offered an ideal mechanism to advance our studies and to assist other investigators in the field.

C. Purpose and Hypothesis:

We are using well-established methods within the CALGB and new procedures developed with support of this project to create a specialized registry which links molecular and epidemiological data with data from uniformly staged breast cancer patients receiving defined therapy. This registry of data, tumor tissue, and other specimens will enhance the research of 30 to 50 peer reviewed and funded investigators during the course of the project. It is intended that the level of quality control as well as the comprehensiveness of the registry will make it an unparalleled

resource for investigators pursuing the relationship between tumor genetics, tumor biology and the prevention and treatment of breast cancer.

D. Methods of Approach - Specific Technical Objectives:

This project creates a linked-registry based upon the capabilities of CALGB to rapidly enroll large numbers of well-characterized incident breast cancer patients. It takes advantage of a unique opportunity to link data on the biology of breast cancer with information on uniformly staged patients who receive defined treatments. Since TNM staging defines rather broad categories[18], especially in stage II breast cancer, we anticipate that an exploration of the sources of heterogeneity with newly developed markers will advance our understanding of the disease.

This registry is used for studies on epidemiological and molecular characteristics that influence the outcome for breast cancer patients. Nested family studies that focus on factors related to etiology will also be possible. The registry will provide information critical to the design of future chemo-prevention studies, the interaction of treatment with factors that govern disease progression and metastasis, and will be instrumental in guiding the design of future adjuvant treatment trials.

Specific technical objectives are as follows:

a. To modify questionnaires currently in use by CALGB investigators at the University of North Carolina, University of Minnesota and NIEHS to collect key family history and exposure data in a self-completed questionnaire.

b. To establish review procedures and criteria for selecting patients with a family cancer history for further study. Criteria will include, but are not limited to, having one or more first-degree relatives with breast cancer or having 2 or more relatives with breast, ovarian, or colon cancer.

c. To develop a telephone interview with patients identified for further study that will expand on the screening data collected, obtain information that will facilitate validation of cancer reported, and locate selected siblings for inclusion in the database. The study will obtain exposure information from affected and unaffected first-degree relatives of patients with a family history of cancer.

d. To collect fixed breast tissue from patients and germ-line DNA, plasma, and urine from the same patients and family members.

e. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

f. To integrate information about specimen receipt, specimen availability, and laboratory testing results with the CALGB data base and to prioritize use of this information.

g. To modify the CALGB data base and data handling procedures at the CALGB Statistical and Data Management Center at Duke University, so as to efficiently capture and record information from the registry, and to furnish it to users.

h. To augment resources at CALGB institutions in order to procure the above described information and specimens.

II. BODY OF THE APPLICATION

A. Description of the Methods:

In contrast to laboratory-based investigations, the linked registry employs new and existing committees of the CALGB and new resources created by the registry to collect specimens, epidemiologic and psychosocial information. It provides a mechanism to integrate registry data with clinical information derived from CALGB clinical trials. Specimens and information from the registry are to be used by laboratory-based investigators, epidemiologists, and others to test various hypotheses bearing on breast cancer cause, risk, progression, response to treatment, as well as to determine the psychosocial impact of this testing.

This project is based at Dartmouth Medical School where Dr. McIntyre, the Principal Investigator, serves as the James Carroll Professor of Oncology, Emeritus. Subcontracts from Dartmouth provide support for activities at the University of North Carolina (DNA extraction and epidemiology), Dana Farber Cancer Center (serum and urine bank), Roswell Park Cancer Institute (tissue sectioning, tissue banking and pathology review), the University of Chicago (communication, protocol editing, and regulatory compliance) and Duke University (statistics and data management). Where possible, efficiencies are achieved by using methods of communication, data submission, protocol editing, meeting arrangements, etc., that have been developed for the CALGB.

The Principal Investigator, Dr. McIntyre, is assisted in the management of the project by three committees:

Table 2
Linked Registry Steering Committee

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	Committee Chair	Dartmouth
Robert Millikan, DVM, Ph.D	Co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
Daniel Hayes, M.D.	Member Breast Com	Dana Farber
Larry Norton, M.D.	Br. Com. Chm	MSKCC
Lauren Schnaper, M.D.	Surgery	U. Maryland
Edison Liu, M.D.	Cor. Sci. Chm.	U. North Carolina
Dale Sandler, Ph.D.	Epi. Com. Chm.	NIEHS

This interdisciplinary committee is responsible for overseeing the conduct of the project, assisting with the integration of projects that will use the registry so as to insure the greatest productivity from it, and setting priorities for use of the resource,

Epidemiology Resource Committee: This committee is responsible for the design of the data collection instruments employed by the linked registry. It will also be responsible for the review and prioritization of projects requesting use of linked registry data. The committee is chaired by Dale Sandler, Ph.D, Chief, Environmental and Molecular Epidemiology Branch, NIEHS, and Chair of the CALGB Epidemiology Committee.

Table 3
Epidemiology Resource Committee

Name	CALGB position	Institution
Dale Sandler, Ph.D.	Chair	NIEHS
Robert Millikan, DVM, Ph.D.	Co P.I.	U. North Carolina
Beth Newman	Epidemiologist	U. North Carolina
Stephanie London MD, PhD	Epidemiologist	Univ. So. Cal.
Matthew Longnecker, MD, ScD	Epidemiologist	UCLA
Thomas Sellers, Ph.D.	Epidemiologist	U. Minnesota
Fred Li, M.D.	Epidemiologist	Dana Farber
Donald Berry, Ph.D	Statistician	Duke University
Virginia Ernster Ph.D.	Epidemiologist	U. of California S.F.
Lauren Schnaper, M.D.	Surgeon	U. of Maryland

In brief, the committee has developed and implemented procedures to collect family cancer history, reproductive and hormone use history, and other exposure information from all breast cancer patients enrolled in CALGB treatment trials. Tumor tissue and germ-line DNA is collected from breast cancer patients as described below.

Breast cancer patients who are registered to CALGB treatment trials are informed by CALGB data coordinators and nurse oncologists about this project at those CALGB institutions where CALGB 9484 has been activated. They are offered the opportunity to participate in a treatment companion protocol that will provide for the collection of epidemiological data and collection of specimens. In order to activate CALGB 9484 institutions must have in place a programmer plans for a program of genetic counseling in order to provide this service to patients who may be found as a result of the project to carry familial breast cancer genes. Those who give their informed consent are offered the questionnaire at the time informed consent for participation in the treatment trial is obtained. We follow all consent procedures mandated by Department of Defense regulations and IRBs at participating institutions. **The self-completed questionnaire is contained in CALGB 9484 included in this report as Appendix 1.**

Questionnaires are collected by the institutional Data Coordinators who submit them to the CALGB Data Management Center at Duke. There, they are examined for completeness, checked for errors, and the data entered in the CALGB data base.

On the basis of information from the self-completed questionnaire, the investigators at UNC, under the direction of Dr. Millikan, categorize the patients into three groups:

a. Patients with any first or second degree relative with breast or ovarian cancer.

b. Patients aged <50 years with no family history

c. Patients aged ≥ 50 years with no family history

All patients in groups a and b, and a random sample of group c, above are contacted by the telephone interviewer. Consenting patients are then queried in the telephone interview. **The questionnaire administered by telephone is furnished in Appendix 2.**

Our previous experience has shown that it is necessary to conduct telephone or in-person interviews to verify and complete family histories and exposure history. Because recall bias is introduced in self-reports of breast cancer occurrence in first degree relatives[19] a carefully administered interview to confirm the self-reporting is indicated. Telephone interviews work as well as in-person interviews for this purpose.[20]

We have found 85% participation rate in our telephone interview inquiring about risk factors for leukemia and this is carried out while these acutely ill patients are hospitalized. While the response rate for the self-completed questionnaires is often lower than that for telephone or in-person interviews, we anticipate a high rate of return of the initial questionnaire because institutional data managers are responsible for retrieving the completed forms. We have used telephone interviews with great success not only in the environmental exposure studies in leukemia patients but also in the long-term follow-up of patients with successfully treated Hodgkin's disease.

Tissue Resource Coordinating Committee: The Breast Tissue Coordinating Committee, Chaired by Dr. Edison Liu, University of North Carolina, serves to coordinate the systematic collection and archiving of breast tissue, germ-line DNA, serum, plasma, and urine.

Table 4
Tissue Resource Coordinating Committee

Name	CALGB position	Institution
Edison Liu, M.D.	Chair	U. of North Carolina
Robert Millikan, DVM, Ph.D.	Co P.I.	U. of North Carolina
Ann Thor, M.D.	Pathology	Vermont Cancer Center
Maurice Barcos, M.D.	Pathology	Roswell Park
Joe Gray, Ph.D.	Genetics	U. of California S.F.
Daniel Hayes, M.D.	Oncology	Dana Farber
Lynn Dressler, M.A.	Tiss. Bank	U. of North Carolina
Hyman Muss, M.D.	Oncology	Bowman Gray
Donald Berry, Ph.D	Statistician	Duke University

1. Fixed tissue:

When the patient signs an informed consent to participate in CALGB 9484 institutional data managers arrange for submission of tissue blocks by contacting the coordinating pathologist at a CALGB main member or affiliate institution. Paraffin blocks and sample submission forms are received at the CALGB Pathology Office directed by Dr. Maurice Barcos at Roswell Park Cancer Institute. There, they are logged into the CALGB data base and histologic sections are made. Four micron slides from these submissions are sent to Dr. Fred Koerner at the Massachusetts General Hospital who reviews them for accuracy of diagnosis, and delineates areas on the slides containing homogeneous malignant tissue. These slides are returned, the blocks trimmed, if necessary, to yield 4 (immunohistochemistry) and 10 micron sections (CPR, FISH) of homogeneous tumor, as well as non-malignant breast tissue. At least 30 ten micron sections are removed and every 10th section will be stained and examined. Sections in flat "ribbons" on wax paper will be stored in the dark at minus 70 degrees C. We ask for permission to retain the blocks for future sectioning and store them at 4 degrees C. If this is not granted, prior to the return of the blocks to the submitting institution we prepare additional sections.

2. DNA procurement:

Somatic DNA: From the specimens collected as described above, individual investigators prepare DNA according to their established laboratory procedures.

Genomic DNA: EDTA anticoagulated peripheral blood is collected and shipped to Dr. Liu's laboratory overnight for leukocyte separation and DNA extraction. Lymphocyte DNA is prepared using the ABI DNA extractor and the DNA stored at -70C.

3. Collection of plasma, serum and urine:

Plasma samples are collected into EDTA-containing collection tubes. After separation from the cellular component, the plasma are aliquoted to a freezing

tube, labeled, and frozen at -20°C at the participating institution. These samples are batched and when several tubes have been collected, they are shipped on dry ice overnight to the Dana Farber Cancer Institute, where they are catalogued and banked at -70°C. Urine samples are collected and stored at 4°C for up to 4 hours before being frozen at -70°C for longer periods. Frozen urine is shipped in batches to the Dana Farber Cancer Institute for processing and analysis.

4. **Training of data managers:**

   On a regular basis, not less than once a year, a portion of the CALGB Data Managers workshop is devoted to instruction of the proper methods of obtaining and shipping the above specimens.

5. **Receipt of Specimens:**

   Centers receiving specimens will electronically report to the CALGB data base the receipt and condition of the specimen using standard CALGB procedures.

6. **Tracking of Patient Specimen Submission:**

   The CALGB data management system tracks patients who are entered on CALGB protocols and generates reminders to institutions that have entered patients on treatment protocols if the required specimens are not received at the appropriate office or lab in a timely manner.

Use of the data from the Linked Registry: All uses for the information in the linked registry will be described in formal protocols that define the objectives, methodology, and statistical assumptions. These must be reviewed and approved by the Steering Committee. **Letters to the users setting out the agreement under which they use the registry are included in Appendix 3.** Written proposals from the scientific community are considered if they do not compete with approved projects already underway, and are prioritized with respect to anticipated amount of tissue or resources consumed vs. the likely yield of important information. In assigning this priority to scientists who are not CALGB members we use the same scale that will be used for projects developed by CALGB members. In all cases emphasis is placed upon the level of innovation and the track-record of the investigator with respect to peer review and publications. We plan to deliberately include projects, however, from young investigators without a track record, if they are endorsed by knowledgeable mentors and are innovative.

The availability of the Linked Registry will be publicized through usual channels of scientific communication. In addition, the CALGB newsletter that is sent to many investigators outside the CALGB will be used as will news releases to "The Cancer Letter", and similar publications.

B. Progress in Year 1.

Modifications in Specific Technical Objectives resulting from negotiation of the final budget for this project.

The project as originally submitted had a budget of $5.1 million. A final budget of $2.0 million was awarded after negotiations concerning a revised project were completed.

We had originally proposed to study 4,500 patients in 4.5 years in this project. Of these, tissue blocks were to have been procured during the 4.5 years on 2,250 patients using support from the Army. In revising the project we have reduced the number of tissue blocks to be collected using Army support to 1,290. We have also projected a slower ramp-up for full activity of the project so as to decrease the number of new hires required during the early phases of the project. This level of staffing is designed to provide for the collection of 170 blocks during the year beginning October 1, 1994, for 510 blocks during each of years 2 and 3, and for 100 blocks during year 4. Thus with a 60% reduction in the original budget, we expect to collect 57% of the originally proposed number of tissue blocks.

We have eliminated the collection breast tissue blocks and other specimens from breast cancer families identified in the course of the project. This task was the most expensive on a per-case basis of those originally proposed and forms a portion of the project that can easily be identified as a separate project. We plan to submit a new grant application that requests funds for this purpose. If funded, this interlocking project would add substantially to the value of the Linked Registry proposal.

As the project stands with the changes in budget we have described above, it proposes to capture comprehensive information and to collect specimens on 1,290 patients over the 4-year period. Since we have recently reported the dramatic interaction of Her-2 and p53 with doxorubicin dose levels in a preliminary study using only 442 patients from CALGB protocol 8541 (see reference 11), there is no doubt that the revised project carried out on 1,290 patients will be successful. Obviously, the larger the number of patients studied, the greater the likelihood of ascertaining various factors interacting in subgroups of breast cancer patients.

Development of a policy on informed consent for genetic testing in this project:

During the design phases of this project prior to submission of our application, we recognized the ethical ramifications of the genetic testing component of our project. Others in the scientific community, particularly those involved in the human genome project, had also faced the need to develop policies in this area. On September 14, 1994 shortly before the award of funds for the project an ad hoc Committee meeting was held to consider the full ramifications studies of familial cancer genes as made possible by the project. Representatives from the genome project, breast cancer patient advocacy groups, the National Institutes of Health, the Office for Protection from Research Risks and relevant committees of the CALGB attended this meeting (See Table 5)

Table 5.
CALGB *ad hoc* Committee on Policy for Genetic Research in Clinical Cancer Trial Patients
September 14, 1994

Participant List

Jeffrey Abrams, M.D.
Cancer Therapy Evaluation Program
Division of Cancer Therapy, NCI

Maurice Barcos, M.D.
Chair, CALGB Pathology Committee
Roswell Park Cancer Institute

Daniel Budman, M.D.
Member, CALGB Breast Committee
North Shore University Hospital

Deborah Collyar
CALGB Breast Committee Advocate
Team Leader Advocacy Core of the SF SPORE

Lynne Dressler
University of North Carolina at Chapel Hill

Helen Felsenthal
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Leslie Ford, M.D.
Acting Deputy Director
Division of Cancer Prevention and Control
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Judy Garber, M.D.
Member, CALGB Correlative Sciences/Solid Tumor Committee
Dana-Farber Cancer Institute

Stephen George, Ph.D.
CALGB Group Statistician
CALGB Statistical Office

Elizabeth Hart
Chair, Susan G. Holman Breast Cancer Foundation Board

Alice Kornblith, Ph.D.
Member, CALGB Psycho-Oncology Committee
Memorial Sloan-Kettering Cancer Center

Patricia Kvochak, J.D.
Deputy, NIH Legal Advisor
Office of General Counsel
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Edison Liu, M.D.
Chair, CALGB Correlative Sciences/ Solid Tumor Committee
UNC - Chapel Hill

Alvin Mauer, M.D.
Member, CALGB Executive Committee
University of Tennessee, Memphis

Robert Mayer, M.D.
Chair, CALGB GI Committee
Dana-Farber Cancer Institute

Ross McIntyre, M.D.
Group Chair, CALGB
CALGB Central Office

Robert Millikan, Ph.D.
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Department of Epidemiology

Sue Moore
External Advisory Board SPORE
Breast Cancer Committee North Carolina

Joan Porter, D.P.A., M.P.H.
Senior Policy Analyst
Office of Extramural Research
Office for Protection from Research Risks
National Institutes of Health

Karen Sartell, M.A.
Group Administrator, CALGB

Natalie Davis Spingarn
National Coalition for Cancer Survivors

Ellen Stovall
National Coalition for Cancer Survivors

Elizabeth Thompson
Coordinator, Genetics Services Research
Ethical, Legal, and Social Implications Branch
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Vincent Vinciguerra, M.D.
Chair, CALGB Cancer Control Committee
North Shore University Hospital Division of Oncology

10/1/94 - 9/30/95
Contract DAMB 17-94-J-4114
O. Ross McIntyre, M.D.

A summary of the recommendations of the *ad hoc* Committee follow:

1. **Informed consent**
   The group agreed that the patient must be informed about the possibility that their tissue, blood or other specimens, will be used research involving high penetrance heritable cancer genes. The patient must have a choice as to whether his/her tissue will be used in this type of research.

2. **Type of consent**
   The group agreed that it would strive for a broad consent with certain caveats: the research conducted by the CALGB would be limited to cancer, confidentiality will be pursued, and there may be some type of disclosure to the subject. Each study would have a consent and disclosure policy tailored for that study. Broad consent is defined as permission to carry out a variety of genetic and other tests, as defined by protocols, which have been approved by IRBs but without the necessity to re-consent the patients for each of the various future tests

3. **Issue of disclosure**
   The group agreed that the subject must have a choice whether he/she wants to learn more about the heritable research. In addition, the disclosure consent must be handled in such a way that the subject is able to change his/her mind at a later date.

4. **Patient confidentiality**
   The group agreed that CALGB must do everything possible to inform patients of the risk of breach of confidentiality to themselves and their family members in view of the existing legal environment. The CALGB will explore the feasibility of obtaining a Certificate of Confidentiality for its studies from the NIH. The patient is the focal point for contacting family members and no family member will be approached regarding participation in heritable or non-heritable research studies without the consent of the patient.

5. **Education of both CALGB members and the CALGB patient population**
   The group agreed that it was essential to educate CALGB members regarding the impact of heritable and non-heritable clinical trials on their patients. The CALGB will have a plenary session on this subject. The mechanisms of educating the patient population will continue to be explored and options include, but are not limited to, counseling, brochures, newsletter, and one on one conversation via an 800 phone number.

   The CALGB should establish criteria for pre and post test counseling and educate its members with respect to the need for counseling before an institution can participate in genetic studies. Education would include types of counseling available locally along with fee schedules.

6. **Oversight of studies investigation heritable and non-heritable cancers**
   The group agreed that the CALGB would establish a mechanism to review trials that include genetic testing within the CALGB organization and that it would consist of both CALGB and non-CALGB members. In addition, all laboratory studies would be

reviewed by an IRB before the study is formally activated. The committee would oversee the ethical conduct of these studies.

7. **Short term goals**
The CALGB would continue to work with the patient advocate groups and other organizations on this subject and would have another meeting toward the end of the year to assess the progress in this area.

Informed Consent Issues:

In addition, the *ad hoc* committee reviewed a draft of the informed consent documents prepared for CALGB protocol 9484, the protocol describing the studies to be supported by the grant from the Army Research and Materiel Command. Considerable input, especially from members of the advocacy community occurred at that meeting and subsequently.

The various parties taking part in this discussion offer divergent views concerning the process for obtaining informed consent, especially with respect to the granting of a broad consent for all future (and as yet, possibly uncharacterized) studies, vs. the need to reconsent the donors of specimens for each laboratory test to which their tissue is subjected. Further the issue of "ownership" of the fixed tissue from the patients is in dispute, with some feeling that the standard consent for surgery used in most institutions conveys control of the tissue to the institution, whereas others feel that the patient retains a residual right.

These complex issues cannot be settled in the context of a single protocol. Our final protocol includes a description of the various viewpoints, and informs the patients that the matter remains unsettled. In this form it has been approved by the Army review process and is being further considered at the level of institutional review boards.

Progress toward meeting Specific Technical Objectives:

a. **To modify questionnaires currently in use by CALGB investigators at the University of North Carolina, University of Minnesota and NIEHS to collect key family history and exposure data in a self-completed questionnaire.**

The self completed patient questionnaire contains items from the above sources and additional input from the team led by Dr. Fred Li at the Dana Farber Cancer Institute has occurred so as to yield a questionnaire that meets the broad needs of investigators. Under the leadership of Drs. Milliken and Ms. Cirrincione a draft self completed questionnaire was developed that addressed the needs of the patients and was capable of being interfaced with the CALGB Data Management System. Pilot testing in CALGB institutions during the early spring of 1995 revealed several problems which were corrected in a further draft that was tested in April. The final version is

incorporated in CALGB protocol 9484 which was mailed to CALGB institutions on May 15, 1995 for activation.

b. To establish review procedures and criteria for selecting patients with a family cancer history for further study. Criteria will include, but are not limited to, having one or more first-degree relatives with breast cancer or having 2 or more relatives with breast, ovarian, or colon cancer.

We have further refined our objectives under this technical objective in order to avoid diluting our efforts given the budget limitations. We will not select allocate those with a family history of colon cancer into the group for the telephone interview. By so doing we will

(i) enrich for BRCA1 and BRCA2 and potentially AT families, rather than diluting our efforts with potential MMR families,

(ii) avoid overlap with a proposed colon cancer susceptibility study supported by other funding

(iii) allow us to focus (as we should) on breast cancer screening and treatment issues, even though colon cancer is an important disease.

The purpose of developing the selection criteria is to yield a pool of individuals with a family history of breast cancer who will participate in an intensive telephone interview. This hour-long interview was developed with input, not only by investigators from this project, but in concert with others who have grants from the U.S. Army Research and Materiel Command, to support related investigations. In addition, a control group of individuals without a family history of breast cancer who are under treatment on CALGB breast cancer protocols is included, as noted above, for comparison purposes.

c. To develop a telephone interview with patients identified for further study that will expand on the screening data collected, obtain information that will facilitate validation of cancer reported, and locate selected siblings for inclusion in the database. The study will obtain exposure information from affected and unaffected first-degree relatives of patients with a family history of cancer.

Ann Davis, PhD. has been recruited to this project at the University of North Carolina and was been part of the team that developed the questionnaire included as Appendix 2. She received her DVM Virginia - Maryland Regional College of Veterinary Medicine in 1994 and is a PhD candidate in the department of Epidemiology at the University of North Carolina. She has experience as a clinical trials coordinator in the pharmaceutical industry and has extensive experience in interviewing patients. As noted above, the interviewing of family members was eliminated from the project as a result

of the need to reduce the budget. The investigators in the project are planning to submit a separate application for grant funds to support this aspect of the project. If funded, the questionnaire described above, will be administered to family members who participate in the project.

d. To collect fixed breast tissue from patients and germ-line DNA, plasma, and urine on the above patients and family members.

CALGB 9484 covering the submission of tissues and specimens listed above, was mailed to CALGB institutions on May 15, 1995. As of September, 1995 the protocol has been approved by the IRBs in 16 institutions listed in table 5.

Table 5
IRB Approval of CALGB Protocol 9484
September 1995

St. Joseph's Hospital and Medical Center, NYH affiliate
Kaiser Permanente CCOP, UCSD
University Medical Center - S. Nevada CCOP, UCSD
Valley Hospital Medical Center - S. Nevada CCOP, UCSD
St. Joseph's Hospital Health Center - Hem/Onc CCOP, Syracuse
Medical Center of Delaware CCOP, UMCC
Beebe Hospital - CCOP, , part of Delaware CCOP, UMCC
Kent General Hospital - CCOP, part of Delaware CCOP, UMCC
Milford Memorial Hospital - CCOP, part of Delaware CCOP, UMCC
Salem County Memorial Hospital - CCOP, part of Delaware CCOP, UMCC
Nanticoke Memorial Hospital - CCOP, part of Delaware CCOP, UMCC
Riverside Hospital - CCOP, part of Delaware CCOP, UMCC
St. Francis Hospital - CCOP, part of Delaware CCOP, UMCC
Union Hospital of Cecil County - CCOP, part of Delaware CCOP, UMCC
University of Tennessee, Memphis
University of Tennessee, Memphis, TN

e. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

This activity will commence in October 1995 as specimens are received.

<u>Infrastructure and Policy Development:</u>

Overview:

During the past year the Pathology Coordinating office has developed an integrated coordination and communication network through the Tissue Resource Coordinating Committee for the systematic collection, archiving, surveillance, quality control and quality assurance for the acquisition and processing of the fixed, paraffin tissue blocks for this study. The appointment of a tissue bank coordinator, who also serves as the CALGB scientific coordinator for solid tumor correlative science studies will facilitate and expedite this integration, interfacing with database management, maintaining appropriate quality control and quality assurance procedures for the storage

and processing of tissues, and developing policies to respond to institutional pathology concerns of tissue banking. In addition, we have identified coordinating/contact pathologists at each of our main and affiliate institutions to expedite case accessioning of paraffin blocks and to establish a network of communication for responding to mutual concerns and problems that may develop during the course of the study (additional efforts to integrate pathology participation are discussed section 3). The following sections describe pathology policy that we have developed for tissue banking (see Section A-2 and Appendix 5), and detailed procedures for processing to ensure quality control and quality assurance (see section B-1 and Appendix 6).

Pathology policy development for tissue banking:

Although tissue acquisition for this study is commencing October, 1995, the pathology office has had experience collecting blocks as a mandatory requirement for four breast cancer clinical trials now active in the CALGB. Because of varying certification and licensing requirements placed at the federal, state and professional society level concerning retention of blocks by institutional surgical pathology laboratories it is not always clear whether all or simply representative tissue blocks are required to remain on file by a pathology laboratory. Some hospital policies prohibit release of an entire block for storage, but will allow cut sections to be stored. Many hospitals are willing to release blocks if they can be assured of accessibility to representative material for any future medical-legal need. In order to address these concerns, and offer alternatives for those hospitals whose policies prohibit release of an entire block for storage we have developed a Tissue Bank policy for this study (Appendix 5).

Quality control and quality assurance of tissue blocks/sections:

Several precautions are taken to ensure that appropriate processing is performed to accommodate a variety of laboratory uses. High quality sections that are representative of the histopathologic diagnosis of breast cancer are required. For example, to reduce possible DNA contamination for molecular assays the following precautions are taken: gloves are worn by the histotechnician, the disposable blade is wiped down with 10% bleach, followed by 70% alcohol between each block unless a new blade is used; the water bath surface is cleaned between each block, clean forceps are used for each block. In addition, all thick, 10 micron sections cut for molecular assays are placed on uncoated slides (to facilitate scraping) and are stored at 4 degrees. All intact blocks are stored at 4 degrees to minimize antigen deterioration. Thin sections cut for immunohistochemistry are stored at a minimum of 4 degrees (preferably -70∞C) and are placed on coated slides (to avoid tissue detachment during assay). H & E sections are cut at different thicknesses throughout the block to ensure that representative tissue is being used for a particular assay. These procedures also address the steps to be taken when minimal tissue is available from the block. This ensures that

tissue will not be exhausted in these blocks. A detailed procedure for processing of tissue sections for molecular, immunohistochemical and flow cytometric assays can be found in Appendix 6.

Efforts to Integrate Pathologist Participation in this Study:

The institutional pathologist is a critical link for accessing representative tissue for laboratory studies. However, in the cooperative group setting, the pathologist has often not participated in breast cancer studies except in the submission of tumor blocks to the Pathology Coordinating Office. In an effort to enhance integration of pathologists into the cooperative research process for breast cancer clinical trials and correlative science studies, we will establish Pathology Workshops at upcoming CALGB meetings to disseminate information regarding breast cancer studies, to discuss the active role that pathologists can play in these studies and provide a forum for problem resolution with respect to accession and tissue banking. The concept of these workshops and pathology integration in cooperation is fully supported by the College of American Pathology. This proposal has been formalized into a grant application to the National Cancer Institute.

f. To integrate information about specimen receipt, specimen availability, and laboratory testing results with the CALGB data base and to prioritize use of this information.

This activity is a major goal for years 3 and 4 of this project.

g. To modify the CALGB data base and data handling procedures at the CALGB Statistical and Data Management Center at Duke University, so as to efficiently capture and record information from the registry, and to furnish it to users.

Under the leadership of Ms. Cirrincione and Debbie Sawyer, the CALGB Data Operations Manager, the first half of the above objective has been met. As information concerning these studies is gathered, the second portion of this task will be performed, namely the integration of the information with clinical characteristics, response to treatment and other endpoints.

Further thinking about the research design has indicated that a goal of furnishing the database information to users is inappropriate. Instead. the results of laboratory and other investigations will reside in the database and will be accessed by CALGB statisticians in order to address hypotheses offered by all investigators participating with CALGB in this project.

h. To augment resources at CALGB institutions in order to procure the above described information and specimens.

Payments to institutions to cover the costs of selecting or obtaining specimens, preparing them for shipment and covering the costs of packaging, will begin as patients are entered on CALGB 9484 during October 1995.

III. SUMMARY

A. Conclusions:

1. CALGB Protocol 9484 providing the basis for specimen and data collection for a Linked Breast Cancer Registry has been approved by the Army Research and Materiel Command, has been circulated to CALGB member institutions, and has been approved by 16 institutional review boards (IRBs). Approval by many more CALGB IRBs is anticipated over the next several weeks.

2. Problems concerning the nature and process of informed consent for studies of familial breast cancer genes have been addressed during the above process and resolved to the extent that a successful project is anticipated.

3. Personnel responsible for the telephone interview of patients concerning risk factors, exposure and reproductive history, and psychosocial data collection have been hired. The procedures used for this purpose have been developed, pilot tested, revised and implemented.

4. The DNA extraction apparatus has been purchased, installed, and tested at the University of North Carolina, Chapel Hill. The freezer for urine and plasma samples has been purchased at the Dana Farber Cancer Institute, Boston and the research technician there has been trained in the procedures necessary for this aspect of the project. Methods for the shipment of specimens, prepaid mailers, and other infrastructure necessary for this aspect of the project have been implemented.

5. A workshop for CALGB data coordinators will be held November 4th in Dallas, Texas in order to further educate CALGB staff as to the requirements of this project.

6. Transfer of the CALGB Central Office to the University of Chicago:

   On March 31, 1995, Dr. McIntyre's 5 year term as Chairman of CALGB was completed and he was replaced as Group Chair by Dr. Richard Schilsky, Director of the University of Chicago Cancer Center, who had been elected to the position. The Central Office of the Chairman moved from Dartmouth College to the University of Chicago during the week of May 8th. Ms. Karen Sartell the Group Administrator and Ms. Mary Sherrell the Chief Financial Officer who played critical roles in this project at Dartmouth continue in these positions in

Chicago and continue their important roles within this project. A new protocol editor in Chicago, Kathleen Karas, has replaced Priscilla Stoner who contributed to this project at Dartmouth. The effort devoted by those in the Central Office to this project has not changed and the positions previously supported at Dartmouth are now supported by a subcontract to the University of Chicago from Dartmouth. Dr. McIntyre continues as Principal Investigator and is linked to the Central Office in Chicago by e-mail, FAX, phone, and by frequent meetings with the staff of the Central Office.

As a result, there has been no material effect of the change in the location of the Central Office upon this project. Nor has there been any change in the time-line as a result of the move of the Central Office. There will be no change in the cost of the project. The same professionals originally awarded support from this project continue their efforts without change and no new professionals are involved in the project. **A letter of support for this project from Dr. Schilsky supporting the project is included as Appendix 7.**

B. <u>Changes Resulting from Experience in Year 1. Problems and Corrective Actions.</u>

The major problem during year 1 has been the delay in activation of CALGB 9484 due to the ethical issues surrounding the studies of familial cancer genes. After much effort a consensus was achieved, though there continue to be well informed and experienced individuals who have not accepted this consensus. Now that the protocol is launched and a number of IRBs have approved it, we anticipate that most institutions will soon approve the protocol. **Appendix 4 is a communication being sent on October 15 to CALGB Principal Investigators and Lead Data Coordinators addressing certain of the questions that have arisen.** Further education efforts will take place at a 3-hour workshop to be held on November 4 during the CALGB Fall Meeting. These education efforts will continue at future meetings. Our experience is that it often takes several months after activation for a CALGB protocol to reach full accrual, and we believe that this will be the case for CALGB 9484.

At this time, we are 170 specimens behind the schedule set out in the budget revision negotiated at the time this project was activated. In order to move the project along at a faster rate it was necessary for us to assign additional personnel at the University of North Carolina who have worked with the staff at the CALGB Pathology Office at Roswell Park Cancer Institute in order to gear up to more rapid receipt of specimens in year 2. In addition, equipment purchases planned for the CALGB Pathology Office will assist in more rapid processing of specimens.

An unexpected number of institutions have requested that the blocks submitted on 9484 be returned immediately after sections have been taken and have cited various regulatory or legal requirements as the reason for these requests. In order to resolve this problem we are taking two courses of action. We hope to convince most of those making this request that it is reasonable for us to have custody of their blocks as long as we demonstrate that we can return them to the institution within one business day of a request for their return. Second, we plan to maintain

paraffin sections in an ultra low temperature freezer instead at the more customary minus 20 degrees C. This may stabilize antigens that have been shown to deteriorate in sections maintained at the higher temperature. A request to rebudget funds from year one for the purchase of the ultra low freezer and other equipment to process blocks efficiently is being submitted.

Dr. I. Craig Henderson, the Chair of the CALGB Breast Committee and a member of the Steering Committee for this project, stepped down from his committee chairmanship in July of 1995. With Dr. Henderson's departure, Dr. Larry Norton of Memorial/Sloan Kettering Institute was appointed to the Chairmanship of the Breast Committee. A long time contributor to CALGB breast cancer science and a participant in the ad hoc committee meeting that made recommendations concerning CALGB policy on studies of heritable genes, Dr. Norton is also taking Dr. Henderson's place on the Steering Committee for this project.

A Certificate of Confidentiality has been requested from the Department of Health and Human Services HHS in order to enhance the level of confidentiality concerning the results of the testing for hereditary cancer genes resulting from this project. Because this project is being conducted on multiple sites there has been a delay in the response of HHS to our request. We will be proposing new wording for the certificate to HHS if our original request is not acted upon soon.

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APPENDIX 1

CALGB Protocol 9484
Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry

Activation Date: June 15, 1995

CANCER AND LEUKEMIA GROUP B

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

CALGB 9484

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1.0 INTRODUCTION

This protocol describes the collection of tumor specimens, genomic DNA, and information concerning medical, reproductive, exposure and family history from patients with breast cancer. The purpose is to create a library in which clinical information on groups of uniformly staged and treated patients on CALGB protocols is located within a structure that also contains patient personal, family, and environmental exposure history, specimens from patients, and data from molecular and other laboratory studies. In contrast to a population-based tumor registry, it offers an internally cohesive group of patients with well-defined disease, treatment and follow-up. It will be possible to draw scientifically valid conclusions from this group by looking for interactions between treatment and factors such as genomic susceptibility and acquired somatic alterations.[1]

We have termed this resource a "linked registry". The registry will be made available to qualified investigators who will conduct a variety of research projects that test laboratory-based, psycho-social or epidemiological hypotheses. These investigators will be supported by peer-reviewed grants and other mechanisms, and the studies will be done at no charge to patients or their participating family members.

In addition, families provide appropriate focused study groups for assessing gene-environment interaction because family members are more highly motivated to provide specimens for study than case controls within the general population. This will provide increased power to detect strong gene-environment interactions in which we are interested.[2] Although family members will not be included in the early phases of this project we will seek funding to support such studies and will use this protocol to collect information and specimens from families when we have secured support to pay for this component of the registry. When this component of the project is underway, we will be able to assess the impact of determining genomic susceptibility on the individuals most in need of this type of information, i.e. members of multiple-case families. Population-based studies are not described in this protocol: with all of the ethical and legal ramifications inherent in population-based genetic studies, we feel that this type of study should come later when specific hypotheses are more fully formed and after we have established the scientific and psycho-social framework for communicating this type of information to the general public.

Ethical and Legal issues relating to studies of heritable genes, and submission of tissue: The consent form for this protocol is based upon policies adopted by the CALGB concerning studies of heritable cancer genes and requires a separate prospective informed consent for genomic DNA submission, as well as a consent for participation in the other components represented. With respect to submission of fixed tissue blocks after diagnosis has been established at the local institution, there are a number of unresolved and sometimes conflicting issues that are currently being addressed by appropriate bodies. The "ownership" of the tissue blocks is felt by some to have been conveyed to the institution by the wording of the usual consent for surgery, but this is disputed by others who feel that, for the purposes represented by the studies to be performed via this protocol, the patient retains rights to the tissue. More particularly, the view has been expressed that the patient may have an enforceable privacy interest when studies are done on tissue that is linked in some manner to them[3]. We believe that the model consent form prepared for participation in the Linked Registry and the Methods section of this protocol specify conditions in which the patient's right to privacy is not subjected to a new risk with each new use of the registry. State laws, the American College of Pathology, the Joint Commission on the Accreditation of Health Care Facilities, and the Clinical Laboratory Improvement Act (CLIA) may have requirements concerning retention of diagnostic tissue at the local institution, and it remains to be determined whether it is permissible under these policies to place the tissue in the custody of other approved parties. Finally, there are divergencies of opinion between the U.S. Army Medical Research and Materiel Command and the

Office of Protection from Research Risks, National Institutes of Health, concerning a requirement that specimens collected with funding from the Department of Defense become the property of the U.S. Government. The consent form informs the patient about the various unresolved issues. Certain of these may require establishment of legal precedent for their resolution.

2.0 OBJECTIVES

1. To collect formalin-fixed, paraffin-embedded (FFPE) breast tissue for in situ studies and extraction of somatic DNA and peripheral blood for extraction of germline DNA, also plasma and urine from patients with breast cancer entered on CALGB breast cancer treatment protocols.

2. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

3. To gather key family, endocrine and reproductive history, and exposure data on the above patients.

4. To prepare and submit the above specimens to approved investigators who will perform various laboratory studies on them and provide the results to the CALGB database for correlation with clinical data and patient outcome.

5. To analyze the data resulting from the above activities in order to seek new knowledge about breast cancer.

3.0 STATISTICAL CONSIDERATIONS

As indicated in Section 7.10 a Steering Committee is responsible for approving each individual project using the resources of the linked registry. Each individual project submitted for review will contain a statistical section detailing the hypothesis and the estimated powers required in the proposed analyses. Flexibility is essential since the alternative hypothesis will vary from one project to the next. If the alternative hypothesis is close to the null, then a large number of patients will be required. A major element in the Steering Committee's review of the proposal will be whether the hypothesis may be adequately tested given the current resources of the registry.

Many of the proposals that we expect to receive will concern analyses of subgroups of patients within the registry. These would be conducted by evaluating an ordered list of scientific hypotheses using sequential statistical tests and would facilitate an early decision on whether a new hypothesis was worth further investigation, while avoiding wasting too much biological material on testing hypotheses that may eventually prove unfruitful. This method will also help to distinguish between a "multitude of hypotheses".[4] The value of the registry to the investigators will be enhanced if it is sufficiently large to allow them to test their hypotheses on subgroups of sufficient size so that adequate power is obtained to detect the differences which are sought. For this reason, the larger the number of patients represented in the linked registry, the more useful the registry will be. It is anticipated that the alternative hypothesis will dictate power, and allocation of resources will proceed sequentially. There is a wealth of material on case only analyses, in which comparisons of cases only (no controls) are used to evaluate gene-environment interactions.[5] We have planned for a registry of up to 5,000 individuals but this number may be adjusted upwards or downwards without amending the protocol depending upon the experience with the various users and the ability to secure funds to operate the registry.

4.0 ELIGIBILITY CRITERIA

4.1 The patient must be enrolled on a CALGB breast treatment protocol. Those protocols from which patients may be entered are listed below. This list will be modified in updates (revisions) to this protocol to include additional CALGB adjuvant or metastatic breast cancer treatment protocols that are activated during the funding period.

9082 A Randomized, Comparative Study Of High Dose CPA/cDDP/BCNU and ABMS Versus Standard Dose CPA/cDDP/BCNU as Consolidation to Adjuvant CAF for Patients with Operable Stage II or Stage III Breast Cancer Involving ≥ 10 Axillary Lymph Nodes

9342 A Phase III Study of Taxol at Three Dose Levels in the Treatment of Patients with Metastatic Breast Cancer

9343 Evaluation Of Lumpectomy, Tamoxifen, and Irradiation of the Breast Compared with Lumpectomy Plus Tamoxifen in Women 70 Years of Age or Older Who Have Carcinoma of the Breast that is Less Than or Equal to 4cm and Clinically Negative Axillary Nodes: A Phase III Study

9344 Doxorubicin Dose Escalation, With Or Without Taxol, As Part Of The CA Adjuvant Chemotherapy Regimen For Node Positive Breast Cancer: A Phase III Intergroup Study

4.2 Patients must sign a consent form agreeing to have their archived tissue blocks, (including somatic DNA but excluding analyses of germline genetic characteristics on associated normal tissues), plasma, and urine submitted for study and to participate in collection of family, exposure and endocrine history questionnaires. **Note:** If the patient also consents to participate in genomic studies, registration must be simultaneous with registration to the treatment protocol and cells for genomic DNA must be obtained prior to the first radiation or chemotherapy treatment. In some instances, depending on the availability of grant funding, close family members (i.e., mother, daughter, sister, aunt) of the patient as described in Sec. 4.1 may also be registered.

5.0 REGISTRATION AND DATA SUBMISSION

Registration will be accepted through the Main Institution only. Confirm eligibility criteria (Sec 4.0). Call the CALGB Registrar (919-286-4704, Monday-Friday, 9 am-5 pm Eastern Time) with the following information:

Your name
Study #
Institution #
Treating Physician
Patient' s Social Security #
Patient' s Name, I.D.#
Patient's Address and Phone Number
Signed Informed Consent (Date)
Type of consent signed: Genomic studies, Non-genomic studies
Race, Sex, Date of Birth
Zip code of residence
Method of payment
Diagnosis, Date of Diagnosis
Eligibility Criteria met (Sec. 4.0) (yes, no)
List CALGB treatment protocol
Does patient release or retain rights to specimens?
Date of most recent Institutional Review Board approval (<1 year)

Registration of eligible family members: The following information will be required:

Your name
Study #
Institution #
Relative's Name
Relationship to Patient
Patient's Name, CALGB #
Patient's Treatment Protocol #
Relative's Address and Phone Number
Date of Signed Informed Consent
Date of most recent IRB approval (< 1 year)

The Main Member Institution will receive a Confirmation of Registration. Please check for errors. Submit corrections in writing to CALGB Data Management Center, First Union Plaza, Suite 340, 2200 West Main Street, Durham, NC 27705.

6.0 REQUIRED DATA

6.1 Submit data forms and specimens according to protocol requirements for all patients registered on CALGB 9484 who receive treatment on an appropriate CALGB breast treatment protocol.

6.2 CALGB institutions should submit specimens along with their corresponding pathology/specimen submission forms to the appropriate CALGB laboratory for storage, as indicated below. If tissue block will not be submitted for a patient, the institution should submit the CALGB Pathology Routing Form (C-350) indicating the reason for nonsubmission along with a letter from the institutional pathologist explaining the reason for nonsubmission.

Copies of these forms are available in Appendix I.

a. Submit tissue block (or letter stating why tissue block will not be submitted), surgical path report and original C-350 form to:

Maurice Barcos, MD, PhD
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263-0001

and a copy of C-350 form to the CALGB DMC; keep a copy for your records.

b. Submit whole blood specimens with original C-383 form to:

Edison Liu, MD
University of North Carolina
Medical Oncology Division
CB #7295 Lineberger Cancer Research Center
Chapel Hill, NC 27599-7295

and a copy of C-383 form to CALGB DMC; keep a copy for your records.

c. Submit plasma specimens with original C-384 form to:

Daniel F. Hayes, M.D.
Dana-Farber Cancer Institute
44 Binney Street
JF526
Boston, MA 02115

and a copy of C-384 form to CALGB DMC; keep a copy for your records.

d. Send Family History of Cancer Questionnaire to the CALGB DMC:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705

6.3 Data Submission:

FORM		Submission Schedule
C-350	CALGB Pathology Routing Form (for tissue blocks) Surgical path report	Submit both form and report regardless of whether or not block is sent. Submit with either tissue block from surgical specimen (breast or node) OR letter from pathologist stating reason for nonsubmission of block. Submit prior to first chemo/RT treatment.
C-383	CALGB Specimen Routing Form (for whole blood)	Submit with whole blood specimens. Submit prior to first chemo/RT treatment.
C-384	CALGB Specimen Routing Form (for plasma)	Submit with plasma specimen. Submit prior to first chemo/RT. For adjuvant studies, submit prior to treatment and at the first follow-up visit after completion of chemo. For metastatic studies, submit prior to treatment and at each follow-up visit scheduled in treatment protocol.
C-377	Family History of Cancer Questionnaire	Within 2 wks of registration onto CALGB 9484. If the patient declines to complete the questionnaire, it should be submitted with "PATIENT DECLINED" and the date written across the top.

7.0 METHODS

7.1 Patient entry: Eligible patients are entered on this protocol if they consent and meet study eligibility requirements given in section 4.0.

7.2 FFPE tissue: A representative block of the primary tumor is best for biologic markers and histologic correlations, but both primary and nodal tissues are acceptable for biologic assays. If insufficient primary or nodal tissue is available for submission of one block, a brief explanatory note from the institutional pathologist within six months of patient entry will suffice.

Submission of representative tissue sections on glass slides is not acceptable since the tissues must be processed in different ways for various assays: 4μ on glass slides for HE staining and immunohistochemistry, 10μ for DNA extraction, and 30μ for nuclear isolation for flow cytometry. The CALGB Pathology Office at Roswell Park Cancer Institute will prepare these sections as there is some evidence that antigen loss may occur over time on cut sections unless maintained at a low temperature.

Each submitted block will be carefully protected and monitored by the CALGB Pathology Office so that depletion of the block is minimized and a minimum of three recut HE sections remain on file at all times. National Institutes of Health directives call for the indefinite retention of each submitted block for future, as yet undetermined, biologic/genetic assays. Upon request for any emergent clinical or legal reason, the remaining portion of the block and one HE section will be returned by overnight mail to the originating Institutional Pathology Laboratory .

Tissue blocks from the operative (not needle biopsy) specimen along with the corresponding surgical pathology report and Form C-350, CALGB Tissue Routing Form must be submitted to:

Dr. Maurice Barcos, Chair
CALGB Pathology Office
Roswell Park Memorial Institute
Department of Pathology
Elm and Carlton Streets
Buffalo, NY 14263
716-845-4443

Institutional data managers will arrange for submission of tissue blocks to the above address by contacting the appropriate pathologist at a CALGB main member or affiliate institution.

Somatic DNA: From the specimens collected as described above, individual investigators will prepare DNA according to their established laboratory procedures. It is anticipated that somatic DNA will be derived from the tumor specimen, but somatic DNA abnormalities may also be sought in normal tissue adjacent to the tumor.

7.3 Collection of plasma and urine: (NOTE 6/15/95: At this time do not submit urine samples. You will be notified when the CALGB is ready to accept urine samples. Whole blood is to be submitted as described below)

7.31 For Adjuvant studies:

If possible collect whole blood and urine samples from patients prior to treatment initiation, and at the first follow-up treatment after the end of adjuvant chemotherapy. Patients may be entered up to three months from registration to the CALGB treatment protocol, but entry prior to treatment is preferable.

7.32 For Metastatic Studies:

Collect whole blood samples from patients prior to treatment initiation and at each follow-up visit scheduled for the treatment protocol.

7.33 Plasma collection and handling:

Collect 10cc of whole blood by venipuncture into an EDTA-containing (purple top) collection tube.

Centrifuge blood at 3000Xg for ten minutes (standard clinical centrifuge). Then aliquot supernatant plasma into a separate tube and label the tube with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered. Special labels are provided.

Separation (centrifuging, aliquoting) the plasma should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

7.34 Urine collection and handling: (Note 6/15/95: Do not collect or ship urine samples until notified.)

Collect 50 ml (or more) clean catch urine into sterile urine collection container.

Centrifuge urine at 200g for 3 minutes (standard clinical centrifuge).

Pour spun urine into plastic freezing tube and label with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered. Special labels are provided.

Separation (centrifuging, aliquoting) the urine should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

Both plasma and urine samples can be stored at -20°C at participating institution until several have accumulated. These samples can be mailed as batches (10-20 specimens or more) on dry ice overnight to the Dana Farber Cancer Institute at the address below.

Be certain that at least five (5) pounds of dry ice are used. Also, ship overnight express so that specimens will not arrive on a weekend or holiday. Remember that certain Massachusetts holidays are not national:

First Monday in October=Columbus Day
November 11=Veteran's Day
3rd Tuesday in April=Patriot's Day (Boston Marathon Day)

Address:

Daniel F. Hayes, M.D.
Dana-Farber Cancer Institute
44 Binney Street
JF526
Boston, MA 02115
Telephone: (617) 632-5404 Fax: (617) 632-3479

7.4 Collection of peripheral white blood cells for Genomic DNA:

Genomic DNA: **Note: A separate consent form must be completed for studies of genomic DNA.** Three tubes of EDTA anti-coagulated whole blood will be collected and shipped overnight to Dr. Liu's laboratory for leukocyte separation and DNA extraction. Lymphocyte DNA will be prepared using the ABI DNA extractor and the DNA stored at -70°C. The methods to be employed are those already in place for studies of ras mutations in leukemic cells by the CALGB.

Ship to:

Edison Liu, M.D.
University of North Carolina
Medical Oncology Division
CB #7295 Lineberger Cancer Research Center
Chapel Hill, NC 27599-7295
Telephone: 919-966-1283

Note: Blood samples should always be sent so that they will be received on a business day. If there are reasons that samples *cannot* arrive except on a weekend or holiday, please call Dr. Liu prior to shipping samples to arrange for receipt.

7.5 Shipment of specimens: After calling the CALGB Registrar to register a patient, the institution should also call the CALGB Central Office at (312) 702-9171 to obtain a Federal Express account number. This account number should be used exclusively for shipment of specimens as detailed above.

7.6 Self-Administered Family History of Cancer Questionnaire: After the patient gives informed consent and is registered to CALGB 9484, the patient will be given a self administered questionnaire covering the above topic. The questionnaire requires about 20 minutes to complete and should be submitted within 2 weeks of entry onto CALGB 9484. The institutional data managers should use the self-addressed envelope to send the completed questionnaires to:

CALGB Data Management Center
2200 West Main Street, Suite 430
Durham, NC 27705
phone: 919-286-0045
Fax: 919-286-1142

The CALGB DMC will forward a copy of the questionnaires to the Linked Registry staff at the Epidemiology Office of the University of North Carolina.

A sub-sample of patients identified on the basis of information provided by the self-administered questionnaire (CALGB Family History of Cancer Questionnaire) will be contacted by the epidemiology office staff at the University of North Carolina, Chapel Hill, and asked to complete a more extensive phone interview (CALGB Detailed Family History and Exposure Telephone Interview). The participating epidemiology staff is funded by a grant, so the phone interviews will be conducted at no charge to patients or their families. Prior to contacting patients by phone, the epidemiology staff will contact the institution that registered the patient to assure that the patient is still alive and not hospitalized, in order to minimize stress to the patient and/or family.

7.7 Receipt of Specimens: A system is being implemented so that Centers receiving specimens will electronically report to the CALGB database the receipt and condition of the specimen using standard CALGB procedures. However, until this system is fully operational, initiating Centers will e-mail or fax this information to the responsible data coordinator at the Data Management Center.

7.8 Tracking of Patient Specimen Submission: The CALGB data management system (or data coordinator, until the system is fully implemented) will track patients who are entered on this CALGB protocol and generate reminders to institutions that have entered patients on this protocol if the specimens are not received at the appropriate office or lab in a timely manner. The CALGB Registrar or automated registration system will remind institutions that patients entering treatment studies are eligible for this protocol if they have not been registered when they are placed on the treatment study.

7.9 Training of data managers: On a regular basis, not less than once a year, a portion of the CALGB Clinical Research Associates workshop will be devoted to instruction of the proper methods of obtaining and shipping the above specimens.

7.10 Linked Registry Policies: Application for use of Registry. Use of the registry is under the supervision of the Linked Registry Steering Committee appointed by Dr. O. Ross McIntyre, M.D. the Principal Investigator on the grant from the U.S. Army Medical Research and Materiel Command which supports the registry. Charter members of the Steering Committee are listed below:

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	Chairman.	Dartmouth Medical School
Robert Millikan, DVM, Ph.D	Co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
I. Craig Henderson, M.D.	Br. Com. Chm	U. California SF
Lauren Schnaper, M.D.	Surgery	U. Maryland
Edison Liu, M.D.	Chm. Cor. Sci.	U. North Carolina
Dale Sandler, Ph.D.	Chm. Epi. Com	NIEHS

Additional members may be appointed to the steering committee from time to time and will be noted in revisions to this protocol. However, it is anticipated that there will be minimal turnover of steering committee membership.

7.10.1 Appendices to Protocol: Appendices to this protocol include laboratory and epidemiological studies that are approved by the Steering Committee for the use of the Linked Registry. Each project will have received IRB approval at the submitting investigator's institution. The appendices will describe their projects in detail, but will not require IRB approval at individual CALGB institutions.

7.10.2 Procedures for Project Approval/Appendix Inclusion: Investigators wishing to use the resources of the registry must apply to the Steering Committee for permission to obtain materials or information from the registry. In each case the investigator must submit a protocol for the proposed study and furnish evidence that it has been reviewed and approved by the Institutional Review Board at the investigator's institution. In addition, the investigator must accept other conditions governing the collaboration. If the investigator is a member of CALGB, usual policies governing Group data management and publication will prevail. If the user is not a member of CALGB, a CALGB co-chair of the proposed study will be appointed by the Steering Committee in consultation with the investigator. The person serving as co-chair will assist in trouble-shooting and will present a synopsis of the status of the study at CALGB meetings, if the non-CALGB investigator is unable to attend. The investigator will be asked to sign a letter outlining the essential features of the collaboration with the Linked Registry. The letter stipulates that the investigator will not provide specimens received from the registry to third parties. These procedures have been put in place in order to: protect patient confidentiality; blind the laboratory doing tests with respect to patient outcomes until the laboratory has submitted its results and the responsible

CALGB statistician has performed an analysis; and achieve agreement on the presentation and publication of results prior to commencing with the work.

It is anticipated that the Linked Registry will be used by a large number of investigators. This protocol will not be amended to describe the details of each laboratory or other use to which an approved investigator may put the Registry, however, as stated above each project using the Registry will have received IRB approval at the investigator's institution. It is anticipated that methodologies in the laboratories will be rapidly evolving during the lifetime of the Registry and that a number of hypotheses will be offered in the future that could not be conceived today. The patients have been given assurance that the Registry will approve studies that are limited to those involving cancer, and it is not intended to reconsent the patient for each new test for which the registry will be used.

Studies of heritable cancer genes will be conducted according to CALGB policies for the studies of such genes. (Appendix III).

8.0 REFERENCES

1. Rothman K. Modern Epidemiology, pp 95-96, Little Brown, Boston, 1986.

2. Khoury M, James L. Population and familial relative risks of disease associated with environmental factors in the presence of gene-environment interactions. Am. J Epidemiol. 137:1241-50, 1993.

3. Charrow RP. Bench Notes- Judgements: Whose Tissue is it, Anyway? Jr. NIH Research, 6: 79-81, 1994

4. Kaaks R, Tweel I, van Noord P, Riboli E. Efficient use of biological banks for biochemical epidemiology: exploratory hypothesis testing by means of a sequential t-test. Epidemiology 5: 429-38, 1994.

5. Begg C, Zhang Z. Statistical analysis of molecular epidemiology studies employing case-series. Cancer Epidemiology Biomarkers & Prevention 3: 173-75, 1994.

9.0 MODEL CONSENT FORMS: LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

9.1 Model Consent Form: Submission of tissue, urine, answering of questionnaire:

Purpose, risks and benefits of this protocol: This protocol is a medical research project involving the collection of additional information about breast cancer in you or your relatives that may not be available in other medical records. The protocol also provides for the submission of the tissue specimens removed at the time of your operation after the diagnostic studies at your hospital are completed. In addition it covers the submission of plasma and urine samples for studies. We refer to this project as a "Linked Registry." You were selected for possible participation in this CALGB study because you are or will be enrolled in one of the CALGB treatment studies in which you will receive systemic drug/hormonal therapy for breast cancer.

This information will be collected on up to several thousand individuals with breast cancer or who are in families that appear to have an increased risk of the disease. The number of individuals involved will depend upon the availability of funding for the registry.

Your decision to participate or not to participate in the Linked Registry project will not affect your medical care. Many investigators who are pursuing a large number of ideas concerning the prevention, cause and treatment of breast cancer will use the resources provided by the registry, but it is unlikely that the new knowledge gained from these studies will have a direct benefit for you. It is likely, however, that the knowledge will assist patients and families in the future.

Participation in this protocol is voluntary. If you choose not to participate or wish to withdraw your consent to participate in this project at any time, it will in no way affect your regular treatments or medical care.

Collection of Urine: Your doctor will be doing routine urine tests. With your approval, about one-half cup of the urine will be sent to a central laboratory for additional tests. These urine samples may be taken only once or up to three times: before you receive your treatment for breast cancer, after you finish your treatment and then 6 months after the treatment is finished.

Collection of Plasma: When whole blood is obtained for routine laboratory tests, and if you agree to participate in this research study, an additional 1 tube of blood, about 1-1/2 tablespoons, will be taken and the plasma sent to a laboratory where it will be stored and used for a variety of tests.

Questionnaire for collection of additional history: A questionnaire that requires about 20 minutes to complete will be offered to you for completion. This will be used to record information about you and your family that is frequently omitted in medical records. Specific questions will address the occurrence of breast cancer in other members of your family, your lifestyle including exercise and diet, use of birth control pills, number of pregnancies, and exposure to substances or agents that might increase the risk of breast cancer. Depending upon the information provided in the questionnaire it may be desirable for us to have additional information. You will be asked to provide your phone number and address on the questionnaire so that you may be contacted by an interviewer for a more in depth series of questions. This interview could take up to 1 hour, although it does not have to be done all at once if it is inconvenient or you are tired. You are not required to answer any question in the questionnaire or interview that you do not wish to complete.

Submission of Tissue: At the time of your surgery for breast cancer you signed or will be asked to sign a consent for the procedure which allows your health care institution to perform diagnostic tests, and to use the tissue for research and educational purposes as well as to discard it. This protocol provides for the collection and use of the portions of tissue not used within your institution so that it may be placed in the Linked Registry and used for research purposes. You should know that there is currently a difference of opinion between various parties including the government that is providing support for the studies, those charged with protecting you from research risks, various state laws, and others as to who may give permission for the tissue to be used for research studies. Rather than awaiting complete resolution of this difference of opinion, the CALGB is requesting that you give permission for inclusion of your tissue and other specimens in the Linked Registry. The U.S. Army Medical Research and Materiel Command which is supporting a portion of the Registry requires that your DNA will become the property of the DNA bank and that a separate consent form be signed indicating this.

CALGB will take measures to comply with the various regulations and laws governing this use of the tissue that is left over from making your diagnosis. It will return any unused tissue from the Registry to your institution, should the need arise.

Methods: Information about the urine, plasma, tissue and information you provide will be maintained in the Linked Registry. You should understand that the value of the Linked Registry is that it will allow scientists to relate tests that have been done on your breast cancer tissue, plasma, and urine to other information about you - for instance, how you responded to treatment, your family history, or your exposure to agents in the environment that might have played some role in the development of your tumor. CALGB will require that all users of the registry provide a written assurance that the data or specimens provided by the registry are used only for the purposes that the Linked Registry Steering Committee has approved, and that specimens or information not be furnished to third parties. In addition, all information about you that includes personal identifiers, will reside in the CALGB database and will be unavailable to the users of the registry. We believe that these measures will adequately protect your right to privacy.

Investigators will use specimens from the registry to test new ideas about the prevention, cause, diagnosis, and treatment of breast cancer. In particular they will be looking for connections between pieces of information in the Registry that may assist in predicting how different people will respond to treatment, or what factors influence whether a tumor progresses and spreads.

You understand that each investigator leading a proposed study of the Linked Registry will first apply to CALGB for permission to use the Registry. You have been told that those in charge of the Registry will choose what studies will be carried out now and in the future. The Linked Registry will be used only for studies on or related to breast cancer. Because it is impossible for you or CALGB to know now what will be discovered in the future and what additional tests may be appropriate then, you have given your permission for such studies without restrictions except as noted in this consent form, and do not wish to be contacted for permission for each specific test. You have been told, however, that each researcher submitting an application for use of your DNA will provide assurance that the research project being proposed has been approved by a review board charged with the protection of the rights of research subjects.

Risks: As described above, CALGB has in place procedures that are intended to maintain your right to privacy. We believe that they are adequate but there is always some risk that your name could be discovered despite our efforts. There is minimal risk to the submission of the urine specimen. When your blood is drawn

you will feel pain but since your doctor will be doing routine blood tests, anyway, there will be no additional risks or discomfort in this study. The amount of blood to be drawn is made up rapidly by the body. You will be inconvenienced because answering the questionnaire will take time. If you are asked to participate in the telephone interview, then that will take an additional hour. It is possible, but not likely, that the telephone interview could cause you some psychological distress. The research interviewer is experienced in this area, however, and will be available to discuss these reactions fully with you.

Patient Protection

You may contact either the investigator in charge or a member of the human protection committee of _____Hospital whose names and phone numbers are listed at the end of this form, if at any point during the duration of this treatment you feel that you have been:

a. inadequately informed of the risks, benefits, or alternative treatments,

or

b. encouraged to continue in this study beyond your wish to do so.

There will be no increased costs to you because of your participation in this study. However, since this study is being supported by funds from the United States Army Medical Research and Development Command, we are required to add the following statement:

"You are authorized all necessary medical care for injury or illness which is the proximate result of your participation in this research. Contractors must provide such medical care when conducting research on private citizens. Other than medical care that may be provided there is no compensation available for your participation in this research study; however, you understand this is not a waiver or release of your legal rights."

The results of this study may be published, but individual patients will not be identified in these publications.

A record of your progress will be kept in a confidential form at _____ Hospital and also in a computer file at the statistical headquarters of the Cancer and Leukemia Group B (CALGB).

Results of your tests, including blood or urine samples and tissue, and confidential information contained in your medical record may not be furnished to anyone unaffiliated with the _____ Hospital or this CALGB project without your written consent, except as required by Federal regulation. Your medical record including identifying information, may be inspected and/or photocopied by the National Cancer Institute or other sponsors of this study, the Food and Drug Administration, or other Federal or state government agencies in the ordinary course of carrying out their governmental functions. If your record is used or disseminated for such purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number, study name and dates. This information is protected by the provisions of the Privacy Act. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the volunteers are adequately

warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

You should understand that research studies of patients may be conducted on other aspects of health care, which may include topics such as the cost and convenience of treatment, and other issues directly affecting patient care. You should also understand that cancer patients and their family members are sometimes asked to complete voluntary questionnaires to assess their quality of life, the inconvenience or cost of care. You understand that Linked Registry personnel may contact you in the future and ask for your permission to participate in such studies.

You will be asked to complete a Background Information Form, to help define groups of patients being treated, so we may better understand the relationship between these groups and results of their treatment. Completion of the form is voluntary and your cooperation is appreciated.

Explanation of use of materials/Possible commercial applications. This research project and its collection and questionnaire procedures have been fully explained to you. You have had the opportunity to ask questions concerning any and all aspects of the project and any procedures involved. By signing below, you grant permission for the use of your bodily fluids, substances and tissues, which may be obtained during testing, operative procedures or other standard medical practices to which you have or will give your consent during the course of your treatment, for use in scientific research, teaching purposes or the development of new tests or products. You understand that there is a possibility that the blood, urine or tissue samples which you are providing as a part of this study may also be used in other research studies and could potentially have some commercial applicability.

You are permitted to retain rights to any commercial application that may arise because of the use of your cells, DNA, or other specimens in this project. Retention of the right, however, increases the cost and paperwork for the institutions that are developing the linked registry and for the granting agencies supporting the use of the linked registry. Because of this you may wish to sign the statement concerning this on the next page.

Your signature indicates that you have read this form, have received acceptable answers to any questions, and willingly consent to participate. You will receive a copy of this form.

_____	_____
(Patient's Signature)	(Date)
_____	_____
(Physician' s Signature)	(Date)
_____	_____
(Witness's Signature)	(Date)
_____	_____
(Responsible Investigator)	(Phone #)
_____	_____
(IRB Representative)	(Phone #)

Study title: **LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY**

Release/Retention of Rights to Specimens

"I voluntarily and freely donate any and all blood, urine and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items." yes____no_____

(Printed Patient Name)	(Patient Signature)	(Date)
(Patient's Address)		
(Printed Physician Name)	(Physician Signature)	(Date)
		(Phone Number)
(Printed Witness Name)	(Witness Signature)	(Date)
Name of IRB Representative	Phone Number	

If you have questions regarding this study you may also call the CALGB Central Office which is located in Chicago, IL. The phone number is (312) 702-9171.

STUDY TITLE: LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

9.2 Model Consent Form: Studies of Heritable (Familial) Cancer Genes by Linked Registry:

CALGB asks your permission to carry out studies of Heritable Cancer Genes. Because such research carries certain risks that go beyond those described in the above consent form, we ask that you give special consideration to the issues involved before agreeing to participate in this part of the Linked Registry.

Risks: The major risk to you in this study is that an inherited change in your genes making it more likely for you to develop breast and perhaps other cancers could be discovered that might make it hard or impossible for you to obtain health insurance or interfere with getting a job. You should understand that CALGB will not release any information concerning this testing to any insurance company or employer unless you request it to do so. Instances are known in which a patient has been *required* to furnish information that would allow access to genetic information as a precondition for application for health insurance and/or a job. CALGB has informed you that it supports legislation current or pending in various states that prohibits discrimination by insurers or employers on the basis of genetic predisposition to disease and which would make it illegal for insurers and employers to inquire whether genetic testing had ever been considered, recommended or performed. The passage of such legislation cannot be assured by CALGB, however.

Depending on the number of individuals in your family who are studied, information regarding your parents may be discovered in the course of this research project. For instance, adoption and/or issues of paternity (fatherhood) may be discovered. You understand that it is CALGB policy not to discuss this particular type of information unless it has direct medical or reproductive implications for you or your family.

Method: As part of providing your care and adjusting your treatment your doctor will be drawing routine blood tests on a regular basis. In addition, with your approval, three extra tubes of blood will be drawn (about 5 tablespoons). This blood will be drawn at the same time as the routine blood tests. You should experience no extra discomfort or side effects.

Certain genes (traits that make up an individual) conferring an increased risk of cancer are passed down from one generation to the next in families. Your DNA will be studied in search for such change in your genes.

You should think about all the issues mentioned above before agreeing to participate in this study. You understand that a genetic doctor or genetic counselor is available to discuss these issues in greater detail to help you and your family think about the potential effects of participation in the study. (Institutions: Please insert name and contact information for genetic counseling here).

Your consent to the study of genes in your blood specimen or in non-cancerous cells that were removed in your biopsy or operative specimen by CALGB will result in them being placed in a bank where the DNA will be used for research studies. Our policy is that these studies will be limited to studies on cancer genes. These will include studies of genes that are passed from generation to generation. Your DNA will become the property of the DNA bank and may be shared with investigators from a number of qualified academic institutions that are studying the genetic causes of cancer.

You understand that each investigator leading a proposed study of cancer genes in specimens from this DNA bank will apply to CALGB for permission to study DNA from you and other patients whose specimens are in the bank. You have been told

that those in charge of the Linked Registry will choose what genetic studies will be carried out on your DNA, now and in the future. You should understand that the value of the Linked Registry is that it will allow scientists to relate tests that have been done on your breast cancer tissue, plasma, and urine to other information about you - for instance, how you responded to treatment, your family history, or your exposure to agents in the environment that might have played some role in the development of your tumor. CALGB will require that all users of the registry provide a written assurance that the data or specimens provided by the registry are used only for the purposes that the Linked Registry Steering Committee has approved, and that specimens or information not be furnished to third parties. In addition, all information about you that includes personal identifiers, will reside in the CALGB database and will be unavailable to the users of the registry. We believe that these measures will adequately protect your right to privacy.

Because it is impossible for you or CALGB to know now what will be discovered in the future and what additional tests may be appropriate then, you have given your DNA to the Linked Registry without restrictions, except as noted on this consent form, and do not wish to be contacted for permission for each specific test. You have been told, however, that each researcher submitting an application for use of your DNA will provide assurance that the research project has been approved by a review board charged with the protection of the rights of research subjects.

You should know that your medical record including possible identifying information, may be inspected and/or photocopied by the National Cancer Institute or other sponsors of this study (including a pharmaceutical company, when relevant), the Food and Drug Administration, or other Federal or state government agencies in the ordinary course of carrying out their governmental functions. CALGB assures you that it will take appropriate measures to separate the genetic information from other information about you in your record, if a request for patient-related information is received from such agencies or sponsors and if unlinking this data is allowed by law and regulations. Further, you understand that CALGB has taken steps to secure a U. S. Public Health Service Certificate of Confidentiality which may further assist in maintaining confidentiality about the results of genetic testing. If your record is used or disseminated for such purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

Costs: We do not think there will be any increased costs because of your participation in this study. However, since this study is being supported by funds from the United States Army Medical Research and Development Command we are required to put in the following statement:

"You are authorized all necessary medical care for injury or illness which is the proximate result of your participation in this research. Contractors must provide such medical care when conducting research on private citizens. Other than medical care that may be provided there is no compensation available for your participation in this research study; however, you understand this is not a waiver or release of your legal rights."

Potential Benefits: The potential benefits of participating in this study are unknown at this time. As the study progresses, the information obtained may be of value to future patients who have breast cancer in helping them select the best treatment for themselves. This study will not alter the treatment you are receiving for your breast cancer.

Explanation of use of materials/Possible commercial applications. This research project and its collection and questionnaire procedures have been fully explained to you. You have had the opportunity to ask questions concerning any and all aspects of the project and any procedures involved. By signing below, you grant permission for

the use of your bodily fluids, substances and tissues, which may be obtained during testing, operative procedures or other standard medical practices to which you have or will give your consent during the course of your treatment, for use in scientific research, teaching purposes or the development of new tests or products. You understand that there is a possibility that the blood, urine or tissue samples which you are providing under this study may also be used in other research studies and could potentially have some commercial applicability.

You are permitted to retain rights to any commercial application that may arise because of the use of your cells, DNA, or other specimens in this project. Retention of the right, however, increases the cost and paperwork associated with the project. Because of this you may wish to sign the statement concerning this on the next page.

If a familial cancer gene is identified in these studies, you have indicated below whether you wish to be contacted concerning results of testing. You have been told that knowledge that a familial change in genes is present in you may help in choosing a schedule of cancer screening and prevention measures that may benefit you if these are carried out. However, you also understand that some changes in genes result in cancers that cannot be prevented or cured with our current knowledge about prevention and treatment. You have weighed the advantages of knowing versus not knowing about your gene status. You also understand that certain of the tests CALGB will use for detection of heritable cancer genes are very new, have not yet been shown to be completely reliable, and may not have been approved by the FDA for diagnostic purposes. If you wish to be informed about the outcome of genetic tests carried out on your DNA, you understand that this information is preliminary in nature, should be investigated further with additional laboratory tests, and is provided to you with these reservations.

I do_____ do not_____ wish to be informed about the outcome of my genetic testing.

Your signature indicates that you have read this form, have received acceptable answers to any questions, and willingly consent to participate. You will receive a copy of this form.

_____	_____
(Patient's Signature)	(Date)
_____	_____
(Physician' s Signature)	(Date)
_____	_____
(Witness's Signature)	(Date)
_____	_____
(Responsible Investigator)	(Phone #)
_____	_____
(IRB Representative)	(Phone #)

STUDY TITLE: LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

Release/Retention of Rights to Specimens

"I voluntarily and freely donate any and all blood, urine and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items." yes____no_____

(Printed Patient Name)	(Patient Signature)	(Date)
(Patient's Address)		
(Printed Physician Name)	(Physician Signature)	(Date)
		(Phone Number)
(Printed Witness Name)	(Witness Signature)	(Date)
Name of IRB Representative	Phone Number	

If you have questions regarding this study you may also call the CALGB Central Office which is located in Chicago, IL. The phone number is (312) 702-9171.

APPENDIX I

Data Collection Forms

C-350 CALGB Pathology Routing Form

C-383 CALGB Specimen Routing Form: Whole Blood

C-384 CALGB Specimen Routing Form: Plasma

INSTRUCTIONS FOR
CALGB PATHOLOGY ROUTING FORM (C-350)

A. Purpose

To provide identifying information that will accompany the slides, paraffin blocks, and pathology report submitted as per protocol.

B. Form-Specific Instructions

Fill in form completely. Do not leave any boxes blank.

1. Enter all information in the upper right box of the page. If the data on this form is an amendment to previously submitted data, please indicate this by writing 'Yes' in the box in the upper right corner of the form, and circle amended data; otherwise, leave this space blank.

2. Record patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.)

3. Code whether the specimen is being sent with this form. If the specimen is not sent be sure to record the reason why it is not being sent (i.e. not enough tissue available, poor specimen quality, etc.). The pathologists at your institution will be able to provide this information.

4. Record the month, day, and 4-digit year that this report is being submitted.

5. Record the number of pathology reports attached.

6. If slides are included, record the number of slides being submitted in the appropriate space. If blocks are included, record the number of blocks being submitted in the appropriate space. This will aid the CALGB pathology office in returning the correct number of specimens to the submitting institution.

7. The full name of the responsible investigator and pathologist and the patient's surgical pathology number at the treating institution should be recorded on the lines provided. This information will further aid in properly identifying the specimen submitted and if there are any questions or problems with the specimen the proper person can be notified.

8. Please provide the complete name of the institution referring the patient. If different from the treating institution, indicate the investigator, pathologist, and patient's surgical pathology number where the original diagnosis was made only if it is different from the treating institution.

9. Sign and date the form.

10. Make two copies of this routing form: keep one for your records, send one to the DMC, and send the original to Dr. Barcos' lab.

Maurice Barcos, M.D., Ph.D.
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, New York 14263-0001
Phone: (716) 845-4443
Fax: (716) 845-8077

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, North Carolina 27705
Phone: (919) 286-0045
Fax: (919) 286-1142

CALGB: PATHOLOGY ROUTING FORM

CALGB Form:	C-350
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____

INSTRUCTIONS: The original of this form is to be completed and submitted along with required slides/blocks and pathology reports. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Please submit a copy to the CALGB Data Management Center.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

---

[1] Specimen: 1. Tissue Blocks/Slides ☐ Does specimen accompany this form? (1-No, 2-Yes)

If ***no***, specify reason: _____
If ***yes***, complete the remainder of this form.

☐☐ ☐☐ ☐☐☐☐ Date pathology report and blocks/ slides submitted
M D Y

☐☐ Number of pathology reports submitted

☐☐ Number of slides submitted ☐☐ Number of blocks submitted

Treating Institution _____

Responsible Investigator _____

Responsible Pathologist _____

Patient's Surgical Pathology Number _____

Institution where original diagnosis was made _____
(Complete only if different from treating institution)

Referring Investigator _____

Referring Pathologist _____

Patient's Surgical Pathology Number _____

Investigator: Make two copies; retain a copy and send a copy to the CALGB Data Management Center and send the original to:

Maurice Barcos, M.D., Ph.D.
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, New York 14263-0001
Phone: (716) 845-4443
Fax: (716) 845-8077

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

INSTRUCTIONS FOR CALGB SPECIMEN ROUTING FORM (C-383): WHOLE BLOOD

A. Purpose

To provide identifying information that will accompany the tube/tubes of whole blood.

B. Form-Specific Instructions

Fill in form completely. Do not leave any boxes blank.

1. Enter all information in the upper right box of the page. If the data on this form is an amendment to previously submitted data, please indicate this by writing 'Yes' in the box in the upper right corner of the form, and circle amended data; otherwise, leave this space blank.

2. Record the patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.).

3. Code whether the specimen is being sent with this form. If the specimen is not being sent, be sure to record the reason why it is not being sent.

4. Record the month, day, and 4-digit year that the tube/tubes of plasma is being submitted.

5. Record the number of tubes of whole blood being submitted.

6. Please refer to the protocol section regarding preparation of the whole blood for shipment to Dr. Liu's lab.

7. Code whether the specimen collected is a pretreatment sample, was collected during treatment or was collected at the follow-up visit. Ship each specimen separately (eg. pretreatment specimen versus during treatment specimen versus follow-up specimen, etc.).

8. Fill in the name of the treating institution.

9. Fill in the full name of the responsible investigator.

10. Sign and date the form.

11. Make two copies of this routing form: keep one for your records, send one to the DMC, and send the original to Dr. Ed Liu's lab.

Edison Liu, M.D.
University of North Carolina
Medical Oncology Division
CB #7295 Lineberger Cancer Research Center
Chapel Hill, North Carolina 27599-7295
Phone: (919) 966-1352
Fax: (919) 966-3015

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705
Phone: (919) 286-0045
Fax: (919) 286-1142

CALGB: SPECIMEN ROUTING FORM:
WHOLE BLOOD

CALGB Form:	C-383
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____

INSTRUCTIONS: The original of this form is to be completed and submitted along with required whole blood specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Please submit a copy to the CALGB Data Management Center.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

[2] Specimen: 2. Whole Blood ☐ Does specimen accompany this form? (1-No, 2-Yes)

If ***no***,specify reason:_____
If ***yes***, complete the remainder of this form.

☐☐ ☐☐ ☐☐☐☐ Date whole blood specimens submitted
M D Y

Specimen Collected

☐☐ Number of tubes submitted

☐ 1. Pretreatment
2. During Treatment
3. At follow-up visit
4. At relapse

Treating Institution _____

Responsible Investigator _____

Investigator: Make two copies; retain a copy and send a copy to the CALGB Data Management Center and send the original to:

Edison Liu, M.D.
University of North Carolina
Medical Oncology Division
CB#7295
Lineberger Cancer Research Center
Chapel Hill, NC 27599-7295
Phone No. (919)966-1352
Fax No. (919)966-3015

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

INSTRUCTIONS FOR
CALGB SPECIMEN ROUTING FORM (C-384):
PLASMA

A. Purpose

To provide identifying information that will accompany the tube/tubes of plasma.

B. Form-Specific Instructions

Fill in form completely. Do not leave any boxes blank.

1. Enter all information in the upper right box of the page. If the data on this form is an amendment to previously submitted data, please indicate this by writing 'Yes' in the box in the upper right corner of the form, and circle amended data; otherwise, leave this space blank.

2. Record the patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.).

3. Code whether the specimen is being sent with this form. If the specimen is not being sent, be sure to record the reason why it is not being sent.

4. Record the month, day, and 4-digit year that the tube/tubes of plasma is being submitted.

5. Record the number of tubes of plasma being submitted.

6. Please refer to the protocol section regarding preparation of the plasma for shipment to Dr. Hayes' lab.

7. Code whether the specimen collected is a pretreatment sample, was collected during treatment or was collected at the follow-up visit. Ship each specimen separately (eg. pretreatment specimen versus during treatment specimen versus follow-up specimen, etc.).

8. Fill in the name of the treating institution.

9. Fill in the full name of the responsible investigator.

10. Sign and date the form.

11. Make two copies of this routing form: keep one for your records, send one to the DMC, and send the original to Dr. Dan Hayes' lab.

Daniel F. Hayes, M.D.
Dana-Farber Cancer Institute
44 Binney Street
D - 1512
Boston, MA 02115
Phone: (617) 632-3472
Fax: (617) 632-3479

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705
Phone: (919) 286-0045
Fax: (919) 286-1142

CALGB: SPECIMEN ROUTING FORM
PLASMA

CALGB Form:	C-384
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____

INSTRUCTIONS: The original of this form is to be completed and submitted along with required plasma specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Please submit a copy to the CALGB Data Management Center.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

[3] Specimen: 3. Plasma

[ ] Does specimen accompany this form? (1-No, 2-Yes)

If ***no***,specify reason:_____

If ***yes***, complete the remainder of this form.

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date plasma specimens submitted

M D Y

Specimen Collected

[ ][ ] Number of tubes submitted

[ ] 1. Pretreatment
2. During Treatment
3. At follow-up visit
4. At Relapse

Treating Institution _____

Responsible Investigator _____

Investigator: Make two copies; retain a copy and send a copy to the CALGB Data Management Center and send the original to:

Daniel F. Hayes, M.D.
Dana Farber Cancer Institute
44 Binney Street
D-1512
Boston, MA 02115
Phone No. (617)632-3472
Fax No. (617)632-3479

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

APPENDIX II

Questionnaires

C-377 CALGB Family History of Cancer Questionnaire

CALGB Detailed Family History and Exposure Telephone Interview

FAMILY HISTORY OF CANCER QUESTIONNAIRE
INSTRUCTIONS FOR CALGB PERSONNEL

A. Purpose - The enclosed survey is part of a recently funded project entitled, "Linkage of Molecular and Epidemiologic Breast Cancer Investigations: A Specialized Registry."

We will be using family history information to select patients for participation in a Registry. The Registry will undertake a systematic collection of tumor specimens, as well as treatment outcome, epidemiologic, and molecular data from breast cancer patients enrolled in clinical trials sponsored by CALGB. Several research hypotheses will be investigated using the Registry, including the role of family history in breast cancer prognosis.

B. Form Specific Instructions

1. Please provide this survey to all patients participating in Protocols _____.

2. We request that the patient complete this questionnaire at the time of treatment with a *RED FELT TIP PEN.*

3. After the questionnaire is complete, return it to the data management representative at your institution.

4. The questionnaires will then be mailed to the CALGB Data Management Center at the following address:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, North Carolina 27705

5. Please try to ensure that all patients on the Protocol are given this questionnaire.

If the patient cannot complete the questionnaire at the time of treatment, they may take it home, but should bring the questionnaire with them at the next treatment.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

Instructions for Patient

Thank you for taking time to complete this confidential questionnaire.

We will ask you about the occurrence of breast and other cancer in your relatives. All of the information you provide on this questionnaire will be held in the strictest of confidence. Neither your name nor any identifying information will appear in any report of the survey.

Based upon your answers to the family history questions, we may wish to contact you again for further information. There is a place on the questionnaire for you to tell us how to reach you in the future. With your help, we hope to learn more about the causes of breast cancer.

At the end of the questionnaire on pages 10 and 11 are comment pages. Use these pages if you need to more fully explain any of your answers. You will also find a space to describe special feelings or insights that you may have about the causes of breast cancer.

If you have any questions about our study or the questionnaire, please feel free to call us toll free at:

1-800-xxx-xxxx Monday - Friday 9 a.m. - 5 p.m.

If a representative is not immediately available, you may leave a message and we will return your call as soon as possible.

When you finish the questionnaire, place it in the envelope provided, and return it to the nurse when she returns to your room.

Thank you very much for your participation.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

INSTRUCTIONS FOR COMPLETING THIS SURVEY

Please proceed with the remainder of the questionnaire. We will be asking questions which require you to provide information about history of cancer in your close relatives.

Make an "X" through the circle which represents your chosen responses with a *RED FELT TIP PEN.*

Example:

Please answer all questions to the best of your ability.

IMPORTANT:

We are asking you about the occurrence of cancer in your full-blood relatives.

We are not referring to step-children, step-siblings, or other half-relations.

If you are adopted and are not able to provide information on blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

Patient's Name_____ Participating Group_____

Patient Hospital Number_____ Participating Group Protocol No._____

Main Member Institution/Adjunct_____ Participating Group Patient No._____

Today's Date

What is your main language: E-English, S-Spanish, O-Other:

(E) (S) (O)

Do you have a phone? N-No,Y-Yes

(N) (Y)

Can we contact you again? N-No,Y-Yes

(N) (Y)

Can we contact you by phone or mail? N-No,Y-Yes

(N) (Y)

Please give us the names, addresses, and phone numbers of two people who will know where you are at all times:

Name:_____

Address:_____

_____

Telephone Number:(___)_____

Name:_____

Address:_____

_____

Telephone Number:(___)_____

What is your present marital status? N- Never Married, M-Married, W-Widowed, S-Separated, D-Divorced

(N) (M) (W) (S) (D)

Are you adopted? Y-Yes, N-No, D-Don't know

(N) (Y) (D)

If "Yes," please read the following:

If you are adopted and you DO NOT KNOW about the cancer history of your blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

We are asking about history of cancer in your blood relatives.

Do you have any full sisters?

(N) (Y) If yes, please specify how many _____

Do you have any full brothers?

(N) (Y) If yes, please specify how many _____

Do you have any daughters?

(N) (Y) If yes, please specify how many _____

Do you have any sons?

(N) (Y) If yes, please specify how many _____

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

Relative		Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other, specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
Example		(X) D U	1	2	3	(X)	5	6	N (X) U	2	2	2	(X)	*Stomach*
1	Mother	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
2	Father	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
3	Sister1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
4	Sister2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
5	Sister3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
6	Sister4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
7	Sister5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
8	Sister6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
9	Sister7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
10	Sister8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
11	Sister9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
12	Sister10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
13	Brother1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
14	Brother2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other, specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
15	Brother3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
16	Brother4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
17	Brother5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
18	Brother6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
19	Brother7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
20	Brother8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
21	Brother9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
22	Brother10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
23	Daughter1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
24	Daughter2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
25	Daughter3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
26	Daughter4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
27	Daughter5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
28	Daughter6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
29	Daughter7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other, specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
30	Daughter8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
31	Daughter9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
32	Daughter10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
33	Son1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
34	Son2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
35	Son3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
36	Son4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
37	Son5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
38	Son6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
39	Son7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
40	Son8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
41	Son9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
42	Son10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

EXTENDED FAMILY

Do you have any other relatives who have been diagnosed with cancer? N-No,Y-Yes

(N) (Y)

If yes please complete the table below:

Relative	Alive or Dead	Type of Cancer
Example: Grandmother	Alive	Ovarian

FAMILY HISTORY QUESTIONNAIRE
COMMENT PAGE

THANK YOU FOR COMPLETING THE FORMAL PART OF OUR QUESTIONNAIRE. BASED UPON YOUR ANSWERS TO THESE QUESTIONS, WE MAY CONTACT YOU IN THE FUTURE. YOU MAY BE ASKED TO PARTICIPATE IN FUTURE STUDIES WHICH ARE AIMED AT INCREASING OUR UNDERSTANDING OF BREAST CANCER. YOUR CONTRIBUTIONS TO THE ON-GOING EFFORT TO UNDERSTAND AND PREVENT BREAST CANCER ARE INVALUABLE TO US.

Please feel free to provide explanations for your answers to any of the preceding questions.

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

COMMENT PAGE

Please use this page to write down any special feelings or insights that you may have about breast cancer. We are interested in what you think may have caused your breast cancer.

CALGB POLICIES GOVERNING GENETIC STUDIES

Whereas studies of somatic mutations in cancer cells pose little risk to the patient, studies of heritable cancer genes may lead to discrimination by insurers and employers. In addition, the discovery of a familial cancer gene carries with it psycho-social consequences which are only imperfectly understood at present and which add to the above risk. For this reason, all consents for studies of heritable cancer genes must be obtained prospectively. These consents should provide adequate information to allow the patient to assess the risk of participation in the study, and should indicate the steps that CALGB is taking to reduce such risks.

Banked material, already obtained from patients on CALGB protocols may be used for studies of heritable genes, but in this case, a reconsent must be obtained from the patient.

The CALGB will take steps to secure, if possible, a Certificate of Confidentiality from the NIH in order to reduce the risk that disclosure of patient identifiers along with information about gene studies will occur.

CALGB will ask its investigators to advocate the passage of state laws preventing insurers and employers from asking for any information about whether the person has had a diagnosis of cancer or whether the person or family members have been the subject of genetic testing.

Because it is unknown what tests may be appropriate on specimens during the time the specimen is banked, the patient will be asked to grant a broad permission for testing. The patient will be informed that heritable gene studies will be limited to those relevant to cancer. The patient will not be asked to grant permission for each individual laboratory study to be performed. Instead, the patient will be assured that all laboratory investigators will have had their project approved by their respective institutional review board prior to receiving permission to study their tissue.

Access to the tissue bank will be granted upon the recommendation of the appropriate committee overseeing the bank. Each investigator using the bank will provide a written description of the project for which the bank is to be used and will be limited to that project. The investigators must agree that all data resulting from their studies will be furnished to the Data Management Center for entry into the CALGB data base. This agreement will also contain provisions for maintaining patient confidentiality. Clinical information from the CALGB data base will not be provided to users of the bank, except in reports prepared by the CALGB which will lack patient identifiers.

Each protocol describing studies of heritable cancer genes will define optimal patient support and set minimum limits for the level of genetic counseling that must be in place in each institution to allow protocol activation.
The CALGB will establish a committee responsible for review of studies involving heritable cancer genes. The charge to this committee is to consider the short and long-term risks associated with protocols involving studies of heritable genes and to advise the Chair with respect to the appropriate actions concerning these studies. The committee is also responsible for reviewing the resources available for genetic counseling at CALGB member institutions and approving these programs as a requisite for institutional participation in designated protocols. This committee will be comprised of CALGB members as well as representatives of the public.

APPENDIX 2

Telephone Interview

BRCA V.6.1

Interviewer ID: _____
Time Interview Began: _____ am/pm
Time Interview Ended: _____ am/pm
Date of Interview: _____
Outcome Code: _____
Reference Date: _____

CALGB DETAILED FAMILY HISTORY AND EXPOSURE
TELEPHONE INTERVIEW

Hello, my name is ANN DAVIS. May I please speak with (RESPONDENT)?
I am calling from the LINEBERGER COMPREHENSIVE CANCER CENTER AT THE UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL. I am calling on behalf of CANCER AND LEUKEMIA GROUP B (CALGB).

A. Recently, you indicated your willingness to participate in a study we are conducting of breast cancer patients. You suggested that this might be a good time to call.
As you recall, we are conducting phone interviews as part of this study. We would like to ask you some questions about your health history. These questions will take about one hour to answer.

Is this still a convenient time for you?

[If NO, reschedule.]

If YES:

Thank you very much. Your answers to these questions will help us to understand the causes of breast cancer.

B. Your cooperation in the survey is entirely voluntary, and all the information collected will be confidential. Neither your name nor any other identifying information will appear in any report of the survey.

C. The interview will take about **60** minutes. First, I would like to verify some of the previous information you have provided to us.

GO TO SECTION A.

A. VERIFICATION OF PREVIOUS INFORMATION
DEMOGRAPHIC INFORMATION

A1. What is your birthdate? ☐☐mm ☐☐dd ☐☐yy

A2.. What is the highest degree or year of school you have completed? (DO NOT READ CATEGORIES)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (PH.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

A3. Would you describe yourself as white, black, Hispanic, Asian, or other? (IF OTHER, PROBE FOR ETHNIC GROUP OR RACE)

[ ] WHITE
[ ] BLACK
[ ] HISPANIC OR MEXICAN AMERICAN
[ ] ASIAN OR PACIFIC ISLANDER
[ ] NATIVE AMERICAN
[ ] OTHER (SPECIFY: _____)

A4. What is your present marital status?

☐ Single
☐ Married
☐ Separated
☐ Divorced
☐ Widowed

A5. IF EVER MARRIED: What is the highest degree or year of school that your husband or partner completed? (DO NOT READ CATEGORIES; IF MORE THAN ONE HUSBAND/PARTNER, ASK FOR MOST RECENT)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (Ph.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

FAMILY HISTORY OF CANCER

A6. Now,I would like to verify the information that you previously provided to us on the Self-Aministered Family History of Cancer Questionnaire.

In this questionnaire, we asked about your full-blood relatives who have been diagnosed with cancer.

I would like to take this time to quickly review the information you provided to us. If you have any corrections or additions to make, please tell me.

[Have a copy of the CALGB Self-Adminstered Family History of Cancer Questionnaire in hand. Verify each relative with cancer for (I) correct diagnosis (ii) relationship to patient. Record any corrections or additions to the previous information below in this copy of the Self-Administered Questionnaire.

Included below: blank copy of Family History Section of Self Administered Questionnaire.]

Now, I would like to proceed with the new questions.
First, I will ask about your Reproductive History.

GO TO SECTION B.

B. REPRODUCTIVE HISTORY

B1. At what age did you start having menstrual periods?

- ☐ Less than 12 years of age
- ☐ 12
- ☐ 13
- ☐ 14
- ☐ 15 years of age or older

B2. Are you still menstruating?

- ☐ Yes
- ☐ No

If "Yes," please go to question B5.

If "No," please continue with questions B3 and B4.

B3. At what age did you have your last menstrual period?

Age ☐☐

B4. Why did you stop having your periods?

- ☐ Periods stopped naturally
- ☐ Surgery (check one):
- ☐ Hysterectomy (uterus and both ovaries removed)
- ☐ Hysterectomy (uterus and one or neither ovary removed)
- ☐ Only ovaries removed
- ☐ Surgery, but not sure what type
- ☐ Chemotherapy
- ☐ Radiation therapy
- ☐ Do not know
- ☐ Other (please explain):_____

B5. Have you ever taken estrogen hormones, such as Premarin, for symptoms or conditions related to menopause (to treat hot flashes, to prevent bone loss, or for other menopausal symptoms)?

☐ Yes
☐ No

If "Yes," proceed with questions B6.

If "No," please go to question B9.

B6. How old were you when you first used hormones/estrogen for symptoms or conditions related to menopause?

Age ☐☐

B7. Are you currently taking hormones/estrogen for conditions related to menopause?

☐ Yes

☐ No

B8.For how many years total have you taken hormones/estrogen?

☐☐ number

B9. Have you ever taken oral progestins (such as Provera) in combination with estrogens for symptoms or conditions related to menopause?

☐ Yes

☐ No

B10. Have you ever taken birth control pills for any reason?

☐ Yes

☐ No

If "Yes," proceed with questions B11.

If "No," please go to questions beginning with C.

B11. How old were you when you first began taking birth control pills?

☐☐Age

B12. Are you currently taking birth control pills?

☐ Yes

☐ No

B13. Keeping in mind that you may have started and stopped several times, for a total of how many years or months did you take birth control pills?

☐ Less than one year

☐ 1 - 3 years total

☐ 4 - 5 years total

☐ 6 - 10 years total

☐ 11 - 15 years total

☐ 16 or more years total

C. PREGNANCY AND FERTILITY

Now I am going to ask you questions about your health. First, I would like to ask you about pregnancies you may have had and any medications you may have taken.

C1. Have you ever been pregnant?

☐ Yes (C2)
☐ No (C23)

C2. How many times, in total, have you been pregnant? (PROBE: Include live births, stillbirths, miscarriages, and induced abortions.)

Number ☐☐

C3. How many liveborn children have you had?

Number ☐☐

C4. Have you had any:		C5. How many?
a) Miscarriages?	[ ] Yes (C5) [ ] No	____
b) Stillbirths?	[ ] Yes (C5) [ ] No	____
c) Induced abortions?	[ ] Yes (C5) [ ] No	____

Now I would like to ask some specific questions about your pregnancies.

		1st preg	2nd preg	3rd preg	4th preg
C6.	What was the result of your (1st/2nd/etc.) pregnancy? (PROBE: Was it a liveborn, stillborn, miscarriage, or induced abortion?)	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know
C7.	How many weeks or months did the pregnancy last?	__ wks OR __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know	__ wks OR __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know	__ wks OR __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know	__ wks OR __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know
C8.	In what month and year did this pregnancy end?	__/__	__/__	__/__	__/__
	LIVEBORN ONLY:				
C9.	Was it a boy or a girl?	Boy Girl Twin girls Twin boys Twin girl,boy	Boy Girl Twin girls Twin boys Twin girl,boy	Boy Girl Twin girls Twin boys Twin girl,boy	Boy Girl Twin girls Twin boys Twin girl,boy
	LIVEBORN ONLY:				
C10.	What was the baby's birthweight?	__/__ lbs oz	__/__ lbs oz	__/__ lbs oz	__/__ lbs oz
	LIVEBORN ONLY:				
C11.	Did you breastfeed this(these) child(ren) for 2 weeks or longer?	Yes No (NEXT PREG)	Yes No (NEXT PREG)	Yes No (NEXT PREG)	Yes No (NEXT PREG)
C12.	How long did you breastfeed this child?	__ wks __ mos __ yrs Still nursing (NEXT PREG)	__ wks __ mos __ yrs Still nursing (NEXT PREG)	__ wks __ mos __ yrs Still nursing (NEXT PREG)	__ wks __ mos __ yrs Still nursing

C13. Did you ever take medication to prevent a miscarriage or to "hold" a pregnancy?

[ ] Yes
[ ] No
[ ] Don't know

	1st	2nd	3rd
C14. Which pregnancy was this?	_____	_____	_____
C15. What was the name of the medication?	_____ Don't know, pills Don't know, shots	_____ Don't know, pills Don't know, shots	_____ Don't know, pills Don't know, shots
C16. How many weeks pregnant were you when you started taking it?	__ __ wks __ __ mos "Early" NOS "Late" NOS Don't know	__ __ wks __ __ mos "Early" NOS "Late" NOS Don't know	__ __ wks __ __ mos "Early" NOS "Late" NOS Don't know
C17. How many weeks or months during this pregnancy did you take it?	__ __ wks __ __ mos Don't know	__ __ wks __ __ mos Don't know	__ __ wks __ __ mos Don't know
C18. Did you take medication to prevent miscarriage or to hold a pregnancy another time?	Yes No	Yes No	Yes No

C19. Was there ever a time in your life when you tried for at least 12 months to become pregnant without being able to?

[ ] Yes
[ ] No

C20. Did you or your husband or partner ever have tests done for fertility?

[ ] Yes
[ ] No

C21. Did the doctor say the problem was due to you, your husband or partner, or both of you?

[ ] Self
[ ] Husband/partner
[ ] Both
[ ] No problem
[ ] Doctor didn't know
[ ] Don't know

C22. Have you ever taken fertility drugs, such as Clomid or Perganol, to stimulate ovulation?
[ ] Yes
[ ] No

	1st	2nd
C23. What was the name of the medication?	_____ Don't know, pills Don't know, shots	_____ Don't know, pills Don't know, shots
C24. In what month and year did you start taking it?	__/__	__/__
C25. For how many months did you take it?	_____	_____
C26. Did you take fertility drugs after that?	[ ] Yes [ ] No	[ ] Yes [ ] No

C27. Have you ever taken birth control pills to either regulate your period or for birth control?
[ ] Yes
[ ] No

	1st PILL USE	2nd PILL USE	3rd PILL USE
C28. In what month and year did you (first/next) begin to use them?	__/__ Don't know	__/__ Don't know	__/__ Don't know
C29. What was the name of the pill you used?	_____ Don't know	_____ Don't know	_____ Don't know
C30. How long did you take them continuously this time?	__ mos __ yrs Less than 1 month Don't know	__ mos __ yrs Less than 1 month Don't know	__ mos __ yrs Less than 1 month Don't know
C31. Did you take birth control pills after that?	Yes (NEXT USE) No	Yes (NEXT USE) No	Yes No

C32. What was the <u>main</u> reason you never used birth control pills?

(CHECK ALL THAT APPLY)
[ ] Doctor recommended against
[ ] Respondent concerned about family history
[ ] Respondent concerned about general safety
[ ] Personal choice, or no need

C33. Are there any other hormone medications that you ever took for any reason, other than those we have already discussed?

[ ] Yes
[ ] No

C34. What was the name of the medication?

_____
[ ] Don't know

C35. For what reason were you taking this medication?

_____

C36. In what month and year did you start taking it?

__/__

C37. For how many months did you take it? ____

C38. Have you have any pregnancies since you were diagnosed with Breast Cancer?

Yes☐
No ☐

C39. What was the outcome?

_____

D. MEDICAL HISTORY

Now I would like to ask you some more questions about your health.

D1. Did a doctor ever tell you that you had any of the following conditions:		D2. How old were you when you were first told you had this?
a) Gallstones or gallbladder disease	[ ] Yes [ ] No	____
b) Severe acne	[ ] Yes [ ] No	____
c) Diabetes (not during a pregnancy)	[ ] Yes [ ] No	____
d) Colon polyps (PROBE: polyps in the colon)	[ ] Yes [ ] No	____
e) Excess body and facial hair	[ ] Yes [ ] No	____

f) Ovarian cyst [ ] Yes [ ] No ____

g) High blood pressure (not during a pregnancy) [ ] Yes [ ] No ____

h) High cholesterol [ ] Yes [ ] No ____

Now I would like to ask you about surgical procedures you may have had before this year.

D2. Did you ever have any surgery to remove any part of your ovaries or uterus?
[ ] Yes (D3)
[ ] No (D5)

D3. How old were you when you had this surgery?
☐☐ Age

D4. After this surgery, did you take any estrogens such as Premarin?
[ ] Yes
[ ] No

Now I'd like to ask you some questions about things that may have happened before you were found to have breast cancer.

D5. Did a doctor ever tell you that you had fibrocystic breast disease?
[ ] Yes
[ ] No

D6. How old were you the first time you were told this?
__ __
Age

D7. Before (1 YEAR PRIOR TO REFERENCE DATE), did you ever have a breast biopsy or aspiration?
[ ] Yes
[ ] No

D8. What was the reason for the breast biopsy or aspiration?
_____

D9. In what year was this done?
_____

D10. What was found?

_____

D11. Before (1 YEAR PRIOR TO REFERENCE DATE), did you ever have any surgery that changed the size or shape of your breasts?

[ ] Yes
[ ] No

D12. Was this surgery to increase the size, or was it to reduce the size or shape?

[ ] Increase
[ ] Reduce

D13. How old were you when you had this surgery?

__
Age

D14. Which procedure was used? (PROBE)

[ ] MASTECTOMY DUE TO CANCER
[ ] PROPHYLACTIC MASTECTOMY
[ ] BIOPSY/LUMPECTOMY
[ ] BREAST PROSTHESIS INSERTED (AUGMENTATION)
[ ] COSMETIC REDUCTION
[ ] OTHER _____

Now I would like to ask you a few questions about when you were diagnosed with breast cancer.

D15. In what month and year were you first told that you had breast cancer?

__/__
(month) (year)

D16. Was your cancer first diagnosed in your left, right, or both breasts?

[ ] LEFT ONLY
[ ] RIGHT ONLY
[ ] BOTH
[ ] DON'T KNOW

D17. How was your breast cancer first discovered: did <u>you</u> first notice a problem, was it found during a routine mammogram, or did you doctor notice a problem?

[ ] SELF-DETECTED
[ ] MAMMOGRAPHY-DETECTED
[ ] PHYSICIAN-DETECTED
[ ] OTHER: _____
[ ] DON'T KNOW

D18. How often have you been screened by Mammography?

☐ At less than 40 years of age

How many times?_____

☐ At age 40-50 years

How often? _____

☐ At greater than 50 years of age

How often? _____

D19. Is this the first time that you have had cancer?

[ ] Yes
[ ] No

D20. In what organ was your first cancer or tumor diagnosed?

_____

(PROBE: What kind of cancer was it?)
(IF SKIN, PROBE FOR TYPE OF SKIN CANCER)

D21. How old were you when this first cancer (NAME OF CANCER) was diagnosed?

Age ☐☐

E. SMOKING

E1. Have you smoked at least 100 cigarettes, that is, 5 packs or more, in your entire life?

[ ] Yes
[ ] No

E2. How old were you when you started smoking cigarettes?

__
Age

E3. Do you smoke cigarettes now?

[ ] Yes
[ ] No

E4. How old were you when you stopped smoking cigarettes?

__
Age

E5. During the years you were smoking regularly, how many cigarettes did you usually smoke per day?

_____
OF CIGARETTES/DAY

F. HEIGHT, WEIGHT, PHYSCIAL ACTIVITY

Now I have some questions that have to do with the time when you were a young teenager, say around 12 years of age or around the 7th grade.

F1. When you were that age, how did your height compare with other girls your age? Were you: shorter, somewhat shorter, about the same, somewhat taller, or much taller?

[ ] MUCH SHORTER
[ ] SOMEWHAT SHORTER
[ ] ABOUT THE SAME
[ ] SOMEWHAT TALLER
[ ] MUCH TALLER

F2. And when you were that age, how did your weight compare with other girls your age? Were you: much thinner, somewhat thinner, about the same, somewhat heavier, or much heavier?

[ ] MUCH THINNER
[ ] SOMEWHAT THINNER
[ ] ABOUT THE SAME
[ ] SOMEWHAT HEAVIER
[ ] MUCH HEAVIER

Now I have a few questions about physical activities when you were around 12 years old. I'd like you to think about 2 different levels of physical activity: vigorous activities, and more moderate activities.

F3. Around this age, did you participate in vigorous physical activities like running, basketball, lap swimming, field hockey, dance, or gymnastics?

[ ] Yes
[ ] No

F4. How often did you participate in vigorous physical activities when you were 12?

__ __ per _____
times day/week/month/year
[ ] Don't know

F5. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

F6. Did you participate in moderate physical activities like recreational volleyball, softball, brisk walking, or leisurely biking when you were 12?

[ ] Yes
[ ] No

F7. How often did you participate in moderate physical activities when you were 12?

__ __ per _____
times day/week/month/year
[ ] Don't know

F8. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

Now let's talk about when you were (in your early 20's/around 20 years old).

F9. How would you describe what your body build was at that age: would you say that you were very slender, about average, a little overweight, or very overweight? (PROBE: Do not include time that you were pregnant.)

[ ] VERY SLENDER
[ ] ABOUT AVERAGE
[ ] A LITTLE OVERWEIGHT
[ ] VERY OVERWEIGHT
[ ] DON'T KNOW

F10. Approximately how tall were you at that age?

__/__ __
ft inches
[ ] Don't know

F11. Approximately how much did you weigh at that age?

___ pounds

Now I have a few questions about physical activities when you were around 20 years old. Again, I'd like you to think about 2 different levels of physical activity: vigorous activities, and more moderate activities.

F12. Around this age, did you participate in vigorous physical activities like running, basketball, lap swimming, or gymnastics?

[ ] Yes
[ ] No

F13. How often did you participate in vigorous physical activities when you were 20?

__ __ per _____
times day/week/month/year
[ ] Don't know

F14. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

F15. Did you participate in moderate physical activities like recreational volleyball, softball, brisk walking, or leisurely biking when you were 20?

[ ] Yes
[ ] No

F16. How often did you participate in moderate physical activities when you were 20?

__ __ per _____
times day/week/month/year
[ ] Don't know

F17. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

Now I have some questions about your weight and level of physical activity in the past ten years.

F18. What has been your lowest weight in the past ten years, not counting this past year?

___
lbs
[ ] Don't know

F19. How old were you (during the past ten years) when weighed that amount?

__ __ yrs old

[ ] Don't know

F20. What is the most that you ever weighed during the past ten years? (PROBE: Do not include any times you were pregnant or nursing.)

___
lbs

[ ] Don't know

F21. How old were you (during the past ten years) when you weighed this amount?

__ __ yrs old

[ ] Don't know

F22. When you gain weight, where on your body do you tend to gain it most easily: below the waist, around and above the waist, or above and below the waist equally? (PROBE: Do not include time when you were pregnant.)

[ ] BELOW THE WAIST
[ ] AROUND AND ABOVE THE WAIST
[ ] ABOVE AND BELOW WAIST EQUALLY
[ ] NEVER CARRIED EXTRA WEIGHT

F23. For the past ten years prior to your diagnosis of breast cancer, please tell me whether you participated regularly in the following activities: (By "regularly" we mean at least 2 hours per week spent in each activity).

[ ] Engaged in heavy manual work, such as digging or chopping with tools, farm or ranch work, construction, scrubbing floors, etc.

[ ] Participation in a sports team, including attendance at practice sessions.

[ ] Participation in individual sports, such as racquet sports, swimming, gymnastics, running/jogging, race walking, bicycling, horseback riding, dance or excercise classes, martial arts.

[ ] Engaged in brisk walking or stair climbing as a part of your work or home activities.

[ ] Participation in light physical activities, such raking lawns, light household chores, walking for pleasure, bowling, golf.

[ ] Other: (explain)

F24. I would like to ask about your participation in these same activities since your diagnosis of breast cancer. Since that time, please tell me whether you participated regularly in the following activities: (Again, by "regularly" we mean at least 2 hours per week spent in each activity).

[ ] Engaged in heavy manual work, such as digging or chopping with tools, farm or ranch work, construction, scrubbing floors, etc.

[ ] Participation in a sports team, including attendance at practice sessions.

[ ] Participation in individual sports, such as racquet sports, swimming, gymnastics, running/jogging, race walking, bicycling, horseback riding, dance or excercise classes, martial arts.

[ ] Engaged in brisk walking or stair climbing as a part of your work or home activities.

[ ] Participation in light physical activities, such raking lawns, light household chores, walking for pleasure, bowling, golf.

[ ] Other: (explain)

G. ALCOHOL USE

The next set of questions is related to beverages that you may have consumed. First, I'd like you to think about when you were in your teens (PROBE: age 16 to 17).

G1. When you were in your teens, that is, around age 16 or 17, was there ever a period where you drank beer, wine, or liquor at least once a week?

[ ] Yes
[ ] No

G2. Did you drink beer at least once a week when you were in your teens?

[ ] Yes
[ ] No

G3. When you drank beer in your teens, how many beers on average did you drink in a week?

_____
[ ] Don't know

G4. Did you drink wine at least once a week when you were in your teens?

[ ] Yes
[ ] No

G5. When you drank wine in your teens, how many glasses on average did you drink in a week?

_____ of _____
glasses/bottle
[ ] Don't know

G6. Did you have drinks containing liquor at least once a week when you were in your teens? (PROBE: Liquor includes things like vodka, whiskey, gin, and brandy.)

[ ] Yes
[ ] No

G7. When you had drinks containing liquor in your teens, how many drinks or shots on average did you have in a week?

_____ of _____
drinks/shots/bottle
[ ] Don't know

Now I would like you to think about when you were (in your early 20's/around 20).

G8. When you were (in your early 20's/around 20), was there ever a period when you drank beer, wine, or liquor at least once a week?

[ ] Yes
[ ] No

G9. Did you drink beer at least once a week when you were (in your early 20's/around 20)?

[ ] Yes
[ ] No

G10. When you drank beer (in your early 20's/around 20), how many beers on average did you drink in a week?

_____
[ ] Don't know

G11. Did you drink wine at least once a week when you were (in your early 20's/around 20)?

[ ] Yes
[ ] No

G12. When you drank wine (in your early 20's/around 20), how many glasses on average did you drink in a week?

_____ of _____
glasses/bottle
[ ] Don't know

G13. Did you have liquor drinks at least once a week when you were (in your early 20's/around 20)?

[ ] Yes
[ ] No

G14. When you had liquor drinks (in your early 20's/around 20), how many drinks or shots on average did you have in a week?

_____ of _____
drinks/shots/bottle
[ ] Don't know

I am now going to ask you about your recent consumption of alcoholic beverages.

G15. In the past five years, have you had at least 10 drinks of any kind of alcoholic beverages?

☐ Yes

☐ No

☐ Never

☐ I no longer drink alcoholic beverages of any kind.

If "Never," please go to section H.

G16. Five years ago, about how often did you drink any kind of alcoholic beverage, including beer, wine, and liquor?

☐ Never

☐ Less than once a month

☐ 1 time a week

☐ 2-4 times a week

☐ Almost every day

G17. Five years ago, what type of alcoholic beverage did you consume most often?

(You may choose more than one type.)

☐ Did not drink during the past five years

☐ Beer

☐ Wine

☐ Liquor

G18. Since your diagnosis of breast cancer, how often do you drink any kind of alcoholic beverage, including beer, wine, and liquor?

☐ Never

☐ Less than once a month

☐ 1 time a week

☐ 2-4 times a week

☐ Almost every day

G19. Since your diagnosis of breast cancer, what type of alcoholic beverage did you consume most often?

(You may choose more than one type.)

☐ Did not drink since diagnosis of breast cancer

☐ Beer

☐ Wine

☐ Liquor

G20. How often do you consume alcoholic beverages now?

☐ Never

☐ Less than once a month

☐ 1 time a week

☐ 2-4 times a week

☐ Almost every day

G21. What type(s) of alcoholic beverage do you consume most often?

(You may choose more than one type.)

☐ Did not drink since diagnosis of breast cancer

☐ Beer

☐ Wine

☐ Liquor

H. PRENATAL INFORMATION

Now, I would like to ask you questions about when your mother was pregnant with you. Perhaps your mother has told you about some of her experiences or things that happened when she was pregnant with you. Please answer to the best of your knowledge.

H1. Did your mother take DES while she was pregnant with you?

[ ] Yes
[ ] No
[ ] Don't know

H2. Did a doctor ever tell your mother that she had diabetes during her pregnancy with you?

[ ] Yes
[ ] No
[ ] Don't know

H3. Did your mother have diabetes when she was younger, that is, before any of her pregnancies?

[ ] Yes
[ ] No
[ ] Don't know

H4. Were you born prematurely? (PROBE: Before 36 weeks)

[ ] Yes
[ ] No
[ ] Don't know

H5. How much did you weigh when you were born?

__ __/__ __
lbs oz
[ ] Don't know

H6. Was this a twin pregnancy?

[ ] Yes
[ ] No

H7. When you were born, did you have any problems or conditions, such as a birth defect?

[ ] Yes (H8)
[ ] No (H9)
[ ] Don't know (H9)

H8. What kind of problem or birth defect did you have when you were born?

_____

H9. Did your mother breastfeed you?

[ ] Yes
[ ] No
[ ] Don't know

H10. Did your mother breastfeed you: less than 3 months, between 3 months and 9 months, or more than 9 months?

[ ] LESS THAN 3 MONTHS
[ ] 3 - 9 MONTHS
[ ] MORE THAN 9 MONTHS
[ ] DON'T KNOW

H11. To the best of your knowledge, when your mother was pregnant with you, did she smoke?

[ ] Yes
[ ] No
[ ] Don't know

H12. When your mother was pregnant with you, did your father smoke?

[ ] Yes
[ ] No
[ ] Don't know

H13. When you were a child, did either of your parents smoke at home?

[ ] Yes
[ ] No
[ ] Don't know

I. VITAMIN SUPPLEMENT HISTORY

NOW I AM GOING TO ASK YOU SOME QUESTIONS ABOUT DIETARY SUPPLEMENTS AND VITAMINS. I WANT TO KNOW IF YOU TOOK OR ARE NOW TAKING THESE SUPPLEMENTS ON A REGULAR BASIS. BY A REGULAR BASIS I MEAN AT LEAST TWO TIMES PER WEEK.

Supplement	Over the past five (5) years, did you take any of the following dietary supplements?		Do you take any of the following dietary supplements now?	
Vitamin A	Yes	No	Yes	No
Vitamin C	Yes	No	Yes	No
Vitamin E	Yes	No	Yes	No
Beta-carotene	Yes	No	Yes	No
Selenium	Yes	No	Yes	No
Iron	Yes	No	Yes	No
Calcium or dolomite	Yes	No	Yes	No
Zinc	Yes	No	Yes	No
Cod Liver Oil	Yes	No	Yes	No
Vitamin B12	Yes	No	Yes	No
Folate or Folic Acid	Yes	No	Yes	No
Multivitamin or Multivitamin with Iron	Yes	No	Yes	No

J. DIETARY HISTORY

J1. Over the past five (5) years, prior to your diagnosis of breast cancer, how often did you eat the following types of foods? (Place "X" in the appropriate boxes.)

Type of food	Never or less than once a week	Once a week	3-4 times a week	Once every day	Twice a day or more
Hamburger or cheeseburger					
Beef steaks					
Chicken					
Pork chops or Ham Steak					
Lamb chops					
Bacon or Breakfast Sausage					
Hot dogs or luncheon meat					
Fish					
Fruits and Vegetables					
Grains (pastas, rice, breads, etc.)					
Dairy (milk, cheese, ice cream, etc.)					

J2. How often do you eat these foods now?

Type of food	Never or less than once a week	Once a week	3-4 times a week	Once every day	Twice a day or more
Hamburger or cheeseburger					
Beef steaks					
Chicken					
Pork chops or Ham Steak					
Lamb chops					
Bacon or Breakfast Sausage					
Hot dogs or luncheon meat					
Fish					
Fruits and Vegetables					
Grains (pastas, rice, breads, etc.)					
Dairy (milk, cheese, ice cream, etc.)					

For the following questions, I am going to ask how often you eat meat, and how you usually prepare meats which you consume.

J3. How often do you eat **beef, pork or lamb** which has been well-browned on the outside by pan-frying or oven broiling?

Never Rarely Sometimes Often

J4. How often do you eat **fish** which has been browned on the outside by pan-frying or oven broiling?

Never Rarely Sometimes Often

J5. How often do you eat **chicken or turkey** which has been browned on the outside by pan-frying or oven broiling?

Never Rarely Sometimes Often

J6. How often do you eat **beef, pork or lamb** which has been charred/blackened by grilling or barbecuing?

Never Rarely Sometimes Often

J7. How often do you eat **fish** which has been charred/blackened by grilling or barbecuing?

Never Rarely Sometimes Often

J8. How often do you eat **chicken or turkey** which has been charred/blackened by grilling or barbecuing?

Never Rarely Sometimes Often

J9. Do you currently follow a **vegetarian** diet?
This means you do not consume beef, pork, lamb, poultry or fish.

☐ Yes
☐ No

J10. Over the past five years, did you follow a **vegetarian** diet for a period of one year or more?

☐ Yes
☐ No

K. MEDICATION HISTORY

I am going to ask about some medications you may have taken in the past and may be taking now. Some of the drugs are over the counter and some are prescription drugs.

K1. The following table refers to over-the-counter and prescription medications you took for any reason.

Medication	Have you ever taken any of the following medications THREE TIMES A WEEK OR MORE for at least ONE MONTH?		Do you take any of the following medications THREE TIMES A WEEK OR MORE now?	
Aspirin or buffered aspirin: Bayer, Anacin, Bufferin, Ascriptin	Yes	No	Yes	No
Ibuprofen: Advil, Nuprin, Motrin IB; Naproxin: Alleve	Yes	No	Yes	No
Prescription anti-inflammatory drugs: Motrin, Feldene, Voltarin, Clinoril, Indocin	Yes	No	Yes	No
Acetaminophen: Tylenol, Panadol, Anacin-3, Dristan AF, Comtrex	Yes	No	Yes	No
BC, Goodys, Emprin, APC powders	Yes	No	Yes	No
Excedrin or Vanquish	Yes	No	Yes	No
Antidepressants or anti-anxiety medications: Prozac, Zoloft, Elavil, Valium, Librium, Xanax, other	Yes	No	Yes	No

L. OCCUPATION

Those are all my questions about your health and your family. My final questions are about jobs that you may have ever had as an adult.

L1. Where were you born? ☐☐ State

L2. Where did you grow up? (You may have grown up in more that one area or state.)

☐☐ State ☐☐ Area
☐☐ State ☐☐ Area
☐☐ State ☐☐ Area
☐☐ State ☐☐ Area

L3. Have you ever been employed outside the home?

[ ] Yes
[ ] No

L4. When you were employed outside the home, what was your usual occupation? (PROBE: That is, what was your complete job title?)

_____

L5. How old were you when you first began working as a (JOB TITLE)?

__ __ years old

L6. Have you ever worked in the field of medical radiation, or ever trained to work in it? Such as X-ray Technician, Dental Hygienist, Veterinarian or Vet Tech?

[ ] Yes
[ ] No
How long? _____
At what age did you begin? _____

L7. Have you every worked in a Lab such as a reference, medical, dental, chemical, or Vet?

☐ Yes
☐ No
How long? _____
At what age did you begin? _____

L8. Have you ever worked or trained as a Beautician?

☐ Yes
☐ No
How long? _____
At what age did you begin? _____

L9. Have you ever worked as a Nurse?

☐ Yes
☐ No
How long? _____
At what age did you begin? _____

L10. Have your ever worked as a managerial or clerical worker?

☐ Yes
☐ No
How long? _____
At what age did you begin? _____

L11. Have your ever lived or worked on a farm?

☐ Yes
☐ No
How long? _____
At what age did you first live there? _____

L12. Was it a farm that had crops?_____ or Livestock?_____or Both?_____

L13. Did you ever use pesticides or herbicides?

☐ Yes
☐ No

L14. Did you ever help mix or apply them?

☐ Yes
☐ No

L15. My last question now is: Have you ever used an electric blanket, or an electric mattress pad, on a regular basis?

[ ] Yes
[ ] No

L14. How old were you when you began using it on a regular basis?

__
Age

M. END OF INTERVIEW

N1. Thank you very much for your help in our survey. Your answers will be very helpful in our research. May we contact you again if we need additional information?

[ ] Yes (I9)
[ ] No (I10)

N2. Could you provide me with the name, address, and phone number of someone who will always know where to get in touch with you?

_____ NAME
_____ ADDRESS
_____ PHONE

N3. Thank you again.

END CALL AND RECORD RESULT CODE AND TIME ENDED ON QUESTIONNAIRE COVER

APPENDIX III

CALGB Policy Governing Genetic Studies

CALGB POLICIES GOVERNING GENETIC STUDIES

Whereas studies of somatic mutations in cancer cells pose little risk to the patient, studies of heritable cancer genes may lead to discrimination by insurers and employers. In addition, the discovery of a familial cancer gene carries with it psycho-social consequences which are only imperfectly understood at present and which add to the above risk. For this reason, all consents for studies of heritable cancer genes must be obtained prospectively. These consents should provide adequate information to allow the patient to assess the risk of participation in the study, and should indicate the steps that CALGB is taking to reduce such risks.

Banked material, already obtained from patients on CALGB protocols may be used for studies of heritable genes, but in this case, a reconsent must be obtained from the patient.

The CALGB will take steps to secure, if possible, a Certificate of Confidentiality from the NIH in order to reduce the risk that disclosure of patient identifiers along with information about gene studies will occur.

CALGB will ask its investigators to advocate the passage of state laws preventing insurers and employers from asking for any information about whether the person has had a diagnosis of cancer or whether the person or family members have been the subject of genetic testing.

Because it is unknown what tests may be appropriate on specimens during the time the specimen is banked, the patient will be asked to grant a broad permission for testing. The patient will be informed that heritable gene studies will be limited to those relevant to cancer. The patient will not be asked to grant permission for each individual laboratory study to be performed. Instead, the patient will be assured that all laboratory investigators will have had their project approved by their respective institutional review board prior to receiving permission to study their tissue.

Access to the tissue bank will be granted upon the recommendation of the appropriate committee overseeing the bank. Each investigator using the bank will provide a written description of the project for which the bank is to be used and will be limited to that project. The investigators must agree that all data resulting from their studies will be furnished to the Data Management Center for entry into the CALGB data base. This agreement will also contain provisions for maintaining patient confidentiality. Clinical information from the CALGB data base will not be provided to users of the bank, except in reports prepared by the CALGB which will lack patient identifiers.

Each protocol describing studies of heritable cancer genes will define optimal patient support and set minimum limits for the level of genetic counseling that must be in place in each institution to allow protocol activation.
The CALGB will establish a committee responsible for review of studies involving heritable cancer genes. The charge to this committee is to consider the short and long-term risks associated with protocols involving studies of heritable genes and to advise the Chair with respect to the appropriate actions concerning these studies. The committee is also responsible for reviewing the resources available for genetic counseling at CALGB member institutions and approving these programs as a requisite for institutional participation in designated protocols. This committee will be comprised of CALGB members as well as representatives of the public.

APPENDIX 3

Letters of Agreement for Registry Users

A. First Letter
B. Application
C. Letter of Approval of Project

Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago IL 60604-1104
TEL (312) 702-9171
FAX (312) 345-0117

Richard L. Schilsky, M.D.
Chairman

Appendix 3.A

Dear _____

Thank you for your inquiry about the CALGB "Linked Registry" This registry incorporates information concerning the staging, treatment and outcome of women treated on CALGB breast cancer protocols and couples this with information concerning risk and prognostic factors. In addition, paraffin embedded tumor tissue, DNA from peripheral blood cells, plasma and urine are available on these patients. This registry is supported by a contract with the U.S. Army Research and Materiel Command and is intended to assist a wide variety of investigations into the causes, prevention, and treatment of breast cancer.

The priorities for the use of the registry are established by the Linked Registry Steering Committee. The Steering Committee current membership is as follows:

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	P.I.	Central Office
Robert Millikan, DVM, Ph.D	co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
Larry Norton, M.D.	Br. Com. Chm	MSKF
Lauren Schnaper, M.D.	Surgery	U. Maryland
Edison Liu, M.D.	Chm. Cor. Sci.	U. North Carolina
Dale Sandler, Ph.D.	Chm. Epi. Com	NIEHS
Lynne Dressler, M.A.	Linked Registry	U. North Carolina

Two advocacy members, (to be named).

Use of the data from the Linked Registry: All uses of the Linked Registry will be described in formal appendices to CALGB protocols. These appendices will define the objectives, methodology, and statistical assumptions to be used in the investigation. Investigators are encouraged to submit requests to use the registry in the format of an appendix to our protocols. These will be reviewed by the Steering Committee at one of its regularly scheduled meetings. If approved by the Steering Committee, the appendices prepared by CALGB Protocol Editors for circulation to the Group institutions and the investigator will receive written permission for use of the registry resources.

If you are interested in using the linked registry, please submit a letter of intent to the Chair of the CALGB Correlative Sciences Committee for Solid Tumors. This letter should outline the proposed investigation and the resources required. Investigators are also encouraged to discuss their proposed project with

members of the Steering Committee. In this way, investigators can be better informed about the current status of the registry and receive input with respect to the feasibility of their request. The Committee Chair will ask those submitting letters of intent consistent with the resources and goals of the registry to prepare a formal application (see below). In addition, the investigators will be invited to describe their projects to those attending the meetings of relevant CALGB Committees which may choose to endorse the proposal and to suggest how it may best proceed within the structure of CALGB.

We point out that users of the registry must agree to follow procedures put in place to protect the privacy of CALGB patients, to insure that CALGB policies concerning data flow and analysis are followed, that responsibility for various tasks related to the project is clearly identified, and that there is agreement with respect to how, where, and by whom the results of the investigation will be reported. These policies and procedures are summarized below. Investigators whose projects have been approved by the Steering Committee must sign a letter in which they agree these provisions before the resources of the registry can be made available to them.

Review of Proposals: Proposals from the scientific community for use of the Linked Registry will be considered if they do not compete with approved projects already underway, and will be prioritized with respect to anticipated amount of tissue or resources consumed vs. the likely yield of important information. In assigning this priority to scientists who are not CALGB members we will use the same scale that will be used for projects developed by CALGB members. In all cases emphasis will be placed upon the level of innovation and the track-record of the applicant with respect to peer review and publications. We will deliberately include projects, however, from promising young investigators, if they are endorsed by knowledgeable mentors and are innovative. The Steering Committee will use an integrated approach to systematically evaluate scientific hypotheses, which implies that projects will be evaluated for their contribution to ongoing avenues of research.

The Steering Committee will evaluate the proposed methods of quality assurance proposed for use during the investigation. Users of the Registry should be aware that peer review of the CALGB has focused on documentation of methods CALGB uses for quality assurance purposes in this type of research.

Again, thank you for your interest. If what you have learned about the registry so far suggests that it would be helpful to you in your research, we look forward to hearing from you.

Sincerely yours,

O. Ross McIntyre, M.D.
Principal Investigator, CALGB Linked Registry.

Enclosure:

APPENDIX 3.B

APPLICATION FOR USE OF CALGB "LINKED REGISTRY" FOR BREAST CANCER RESEARCH

Date:
Name:
Address:
Institution:
Position/Department

Title of Project:

Hypothesis: [50 words or less]

Attach the following to your application:

Background: [250 words or less]

Specific Aims: [list no more than three. 100 word limit]

Methods: [Provide general description of methods with particular attention to what resources you need from the linked registry. Include description of number and type of samples. Justify with a statistical section. Discuss your plan with CALGB statistician and Chair of the CALGB Committee for Correlative Sciences in Solid Tumors prior to writing this section. Specify the analyses that will be performed using clinical, epidemiologic or other resources from the registry. Two page limit]

Significance: [250 words or less]

Attach Biosketch or CV. Indicate active peer reviewed grants that will be supporting this work or other support for this work. The Linked Registry has no funds to support individual projects.

Policies governing the use of the Linked Registry: The following text will be included in a letter which CALGB will furnish to the investigator who must sign and return it prior to activation of the project:

"This is a collaborative project between you and the Cancer and Leukemia Group B (CALGB). The usual ground-rules for collaborations of this type will prevail. Data from all laboratory tests performed on samples from the registry will be submitted by you to the CALGB Data Management Center. In the usual situation transfer of this data will be via electronic means. At the Data Management Center it will be entered into the CALGB Database for analyses specified in the research plan. These analyses will be conducted by the relevant

CALGB statistician. You agree that all analyses reported from your project will be based upon data contained in the CALGB Database.

Tissues and other samples are furnished to you by the Linked Registry for the purpose of the project as approved by the Steering Committee. You agree to limit your research to that described in your application unless written approval to change the scope of your investigation is obtained from the Steering Committee. You also agree that you will not furnish materials from the Linked Registry to other parties for any purpose without the written approval of the Steering Committee.

As the lead investigator, it is expected that your name will be listed as the first or last author of publications coming from this project. Other members of your research team may be granted authorship, as appropriate. CALGB personnel, usually the CALGB statistician assigned to this project, relevant members of the steering committee who are responsible for the resource used in the investigation, and others making significant intellectual contributions, will be included as authors. You will acknowledge the support of the Linked Registry Contract from the Army along with the disclaimer " Opinions, interpretations, conclusions, and recommendations expressed in this publication are those of the authors and not necessarily endorsed by the U.S. Army". You will provide the CALGB Central Office with draft copies of manuscripts 30 days prior to submission and abstracts at least 5 days prior to submission, for comment by the CALGB.

If you are not a member of CALGB but are based within a CALGB institution, you may ask that the CALGB Principal Investigator at your institution enter you on our roster. In this way you will be provided with information concerning Group activities that may bear on your project. If you are not at a CALGB institution we will enter your name in the CALGB roster as a " colleague" and ask you to choose a CALGB member as a co-investigator. If you need help in this task, please discuss this with the Chair of the Correlative Sciences Committee for Solid Tumors. The co-investigator will assist with trouble shooting problems within CALGB that may arise during the course of your investigation and will provide other assistance. Ordinarily, the co investigator will also be an author on publications.

The Steering Committee in carrying out its responsibilities for the operation of the Registry will from time to time monitor all projects using the resource. The productivity of ongoing projects and adherence to scientific and ethical standards set by the CALGB will be assessed in this review.

Please submit your proposal in the above format to
CALGB Central Office
208 South LaSalle Street, Suite 2000
Chicago, IL 60604-1104

Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago IL 60604-1104
TEL (312) 702-9171
FAX (312) 345-0117

Richard L. Schilsky, M.D.
Chairman

Appendix 3.C

Dear _____

I am pleased to inform you that your research plan has been reviewed and approved by the Steering Committee for the CALGB Linked Registry. The Protocol Editor assigned to this study is _____. He/She will be contacting you with respect to any final editing necessary to put the appendix into final form for submission to CALGB institutions. In order for this protocol to be activated we must ask that you sign and date the both copies of this letter. Keep one for your files and return the other to the your protocol editor.

We apologize for the formality of this procedure, but we have found that written understandings of what collaboration has been agreed to is in the interest of both parties. The following text describes the nature of this collaboration :

"This is a collaborative project between you and the Cancer and Leukemia Group B (CALGB). The usual ground-rules for collaborations of this type will prevail. Data from all laboratory tests performed on samples from the registry will be submitted by you to the CALGB Data Management Center. In the usual situation, transfer of this data will be via electronic means. At the Data Management Center it will be entered into the CALGB Database for analyses specified in the research plan. These analyses will be conducted by the relevant CALGB statistician. You agree that all analyses reported from your project will be based upon data contained in the CALGB Database.

Tissues and other samples are furnished to you by the Linked Registry for the purpose of the project as approved by the Steering Committee. You agree to limit your research to that described in your application unless written approval to change the scope of your investigation is obtained from the Steering Committee. You also agree that you will not furnish materials from the Linked Registry to other parties for any purpose without the written approval of the Steering Committee.

As the lead investigator, it is expected that your name will be listed as the first or last author of publications coming from this project. Other members of your research team may be granted authorship, as appropriate. CALGB personnel, usually the CALGB statistician assigned to this project, relevant members of the steering committee who are responsible for the resource used in the investigation, and others making significant intellectual contributions, will be

included as authors. You will acknowledge the support of the Linked Registry Contract from the Army. You will provide the CALGB Central Office with draft copies of manuscripts 30 days prior to submission and abstracts at least 5 days prior to submission, for comment by the CALGB.

If you are not a member of CALGB but are based within a CALGB institution, you may ask that the CALGB Principal Investigator at your institution enter you on our roster. In this way you will be provided with information concerning Group activities that may bear on your project. If you are not at a CALGB institution we will enter your name in the CALGB roster as a " colleague" and ask you to choose a CALGB member as a co-investigator. If you need help in this task, please discuss this with the Chair of the Correlative Sciences Committee for Solid Tumors. The co-investigator will assist with trouble shooting problems within CALGB that may arise during the course of your investigation and will provide other assistance. Ordinarily, the co investigator will also be an author on publications.

The Steering Committee in carrying out its responsibilities for the operation of the Registry will from time to time monitor all projects using the resource. The productivity of ongoing projects and adherence to scientific and ethical standards set by the CALGB will be assessed in this review. You agree to abide by the decisions of the Steering Committee that may come from this review.

Thank you very much and good luck with your investigation.

Sincerely yours,

O. Ross McIntyre, M.D.
Principal Investigator, Linked Registry Project

I agree to the terms of this collaboration.

Signed

_____ Date_____

name

APPENDIX 4

Letters to CALGB Institution
Questions & Answers on 9484

CANCER AND LEUKEMIA GROUP B

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality Chairs, Executive Committee, Statistical Office, Data Management Center, and QARC

From: O. Ross McIntyre, M.D., Study Chair

Subject: **CALGB 9484:** LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

Date: October 15, 1995

Sixteen IRBs have now approved CALGB 9484. Several questions have arisen during the review and activation of this protocol. This memorandum responds to the questions and also includes an invitation to you and your staff to attend a workshop during the upcoming Group meeting on Saturday evening, November 4, 1995, 6:30-9:30 p.m., where we will be discussing a variety of issues concerning studies of heritable cancer genes. Please return the enclosed form concerning genetic counseling in your institution(s) so that we may better design a program of workshops to support CALGB studies.

Commonly asked questions:

1. Is there institutional support for this protocol?

Yes. The grant from the army will reimburse institutions $275 for each patient on study. These funds are meant to defray the costs of selecting the tissue blocks, preparing them for shipment, obtaining informed consent for the genetic studies, etc.

2. Is it necessary for an institution to have an approved genetics counseling program in place for 9484 to be activated?

No. It is necessary, however, for the institution to have plans to develop a means to provide counseling concerning heritable cancer genes at some time in the future. It is not known when the results of the testing done on specimens obtained on this protocol will be available, but it will probably be in one or two years.

3. Will CALGB provide genetic counseling?

No. CALGB will not provide genetic counseling. However, CALGB will assist in training of institutional staff and the development of institutional capabilities in this area. It is likely that commercially available tests for familial cancer genes will be available in approximately a year, and institutions will need to develop strategies to address counseling needs related to these commercial tests. The army -supported CALGB project can assist your institution as it prepares for this new area of clinical genetics.

4. Our institution lacks a genetic counselor. Can others provide the necessary information to the patient?

Yes. Each institution is responsible for developing a program appropriate for that institution. Counseling could be provided by any individual with an appropriate background and training in the area.

5. Can the institution use some of the $275 per patient reimbursement to support an institutional genetics counselor attending the workshop?

Yes. The funds may be used for any purpose that contributes to the success of 9484 in your institution.

6. Some individuals in our institution wish to rewrite the model consent form. We feel patients should not be informed of the results of the testing. Can we rewrite the consent form?

Yes. As long as your consent form contains the necessary elements of informed consent, CALGB will not object. You and your institution should know, however, that the model consent form was extensively discussed and revised by a large ad hoc committee that included experts in human molecular genetic studies, genetic counselors, advisors from the Office for Protection from Research Risks (OPRR), breast cancer experts, and members of cancer patients advocacy groups. If you or your IRB wish access to the minutes of that meeting you should contact the CALGB Central Office.

It is most important that we get this protocol off to a good start. If additional questions arise, please don't hesitate to contact me at my CALGB e-mail address (O.Ross.McIntyre@Dartmouth.EDU).

Thank you very much,

APPENDIX 5

Tissue Banking Policy for Paraffin Blocks
in the Linked Tumor Registry

Appendix 5

TISSUE BANKING POLICY FOR PARAFFIN BLOCKS IN THE LINKED TUMOR REGISTRY:

General Policy:

1. All precautions are taken to prevent exhausting tissue on the block.
2. A minimum of three H & E sections (obtained at different thicknesses) will remain on file at the CALGB Pathology office and are available to the submitting institution if needed.
3. A minimum of 2 unstained sections will remain on file and will be available to the submitting institution if needed.
4. Whenever there is an immediate medical or legal need, the unused tissue, along with an H & E section will be returned by overnight mail to the submitting institution.

Standard Tissue Processing:

It is optimal to obtain and bank the entire tissue block so that tissue can be sectioned freshly as needed, as certain antigens (e.g. p53) and other components deteriorate over time when tissue is pre-cut and stored as thin sections. Since it is impossible to predict the effect that extended storage might have on the detection of future markers, a consensus was reached at a recent NCI Inter group Tissue Banking meeting, that tissues be ideally sectioned freshly as needed for biologic makers. Blocks that are submitted to the CALGB pathology office are maintained in a secure space and appropriately recorded into our database. The CALGB is expending significant resources to establish and maintain a tissue surveillance database, expand physical storage capacity and optimize storage conditions for optimal monitoring and quality control for processing, storage and utilization of these tissues. Utilization of tissues occurs only after the proposed scientific study has received approval from the Steering Committee and Solid Tumor Correlative Science committees. Blocks are sectioned freshly for the appropriate assay and are processed in different ways and with special precautions: e.g.. for immunohistochemical studies, 4micron sections on coated slides are prepared and maintained at 4 degrees or colder (-70 degrees is preferable); for DNA extraction studies, 10 micron sections on uncoated slides are prepared carefully to prevent DNA contamination (stored at 4 degrees) and for flow cytometric studies, 3, 50 micron sections are prepared (stored at 4 degrees), in which tumor rich areas are separated from tumor poor areas.

Expedited Tissue Processing:

Although it is optimal to bank blocks so that tissue can be sectioned freshly as needed, we realize that various situations may preclude institutional block submission for banking purposes (institutional policies, legal requirements, minimal embedded tissue). If , for these reasons, a block cannot be maintained in the CALGB Tissue Bank, we ask you to consider submitting the corresponding block for a period of 2-8 weeks, during which time the CALGB pathology office

will expedite tissue processing according to the above guidelines, store the sections at 4 degrees or colder (-70 degrees is preferable) for utilization in companion trials (that do not incorporate labile antigens) and return the blocks to your laboratory.

Institutional Tissue Processing:

Because this material is of great importance for the conduct of CALGB Correlative Science studies and the future direction of our treatment protocols, we would also ask those institutions whose policies prohibit the release of any block from their institution to consider cutting the sections at their own institution. A detailed procedure for sectioning of the specimens can be sent to your laboratory. If needed, we will cover the cost of shipment of the cut sections to the CALGB pathology office. However, as detailed above, sectioning requires special dedication and precautions to prevent cross-contamination from a histotechnician and you may want to reconsider release of the block(s) for a 5 day turn around during which we will expedite the tissue sectioning from these cases.

APPENDIX 6

Pathology Quality Control
and Quality Assurance

APPENDIX 6

PATHOLOGY QUALITY CONTROL AND QUALITY ASSURANCE

Procedure for Cutting Sections for the Linked Registry:

I. Quality assurance:

A. Histotech should wear gloves to prevent DNA contamination

B. Disposable blade should be changed between each block
or
Wipe down blade with 10% bleach, followed by 70% alcohol between each block

C. Clean water bath surface between each block to prevent contamination

D. Clean forceps or other instruments used for separating ribbon between each block

E. All 10 micron sections should be placed on uncoated slides and stored at room temp.

F. All 4 micron sections should be placed on superfrost+ coated slides.*

1. H & E sections should be stored at room temperature

2. All other 4 microns sections should be stored in a slide box at 4 degrees.

G. Do not place any cut sections on the slide warmer tray.

II. Sequence of sectioning:

Overall:

top H & E section-coated slide

20, 4 micron sections-coated slide (IHC)

middle H & E (a) section- coated slide

10, 10 micron sections-uncoated slides (Molecular)

middle H & E (b) section - coated slide

3, 50 micron sections- in screw-top glass tubes (Flow Cytometry)

bottom H & E section- coated slide

Labeling:

label all sections with specific pathology block number

label all sections with clinical protocol number and patient protocol

number; indicate group (ECOG, SWOG, CALGB, etc.)

number serial sections (1-20 for 4 micron; 1-10 for 10 micron)

indicate date that sections were cut: "cut date 00/00/00"

top H & E section: label "top"

middle H & E sections: ;label "middle a"; " middle b"

bottom H & E section: label "bottom"

A. Optimal sequence:

1. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining. (label "top")
2. Cut 20, 4 micron sections on coated slides-place in slide box, store at 4 degrees.
3. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "middle" a)
4. Cut, 10, 10 micron sections on uncoated slides-place in separate slide box and store at room temperature.
5. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "middle b")
6. Cut, 3, 50micron sections, place curled sections in a screw top glass tube
7. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "bottom")

B. When minimal tissue is available: omit the 50 micron sections for flow cytometry first, then if there is still insufficient tissue to cut the 20 4micron sections for IHC and 10, 10micron sections for molecular; follow the following procedures (each level indicates less tissue available for cutting):

Level I.: (10, 4u;5,10u)

1. Cut top H & E section (coated slide).
2. Cut 10,4 micron sections (coated slide)
3. Cut middle H & E section (coated slide)
4. Cut 5, 10 micron sections (uncoated slide)
5. Cut bottom H & E section (coated slide)

Level II:(5,4u; 3, 10u)

1. Cut top H & E section (coated slide)
2. Cut 5,4 micron sections (coated slide)
3. Cut middle H & E section (coated slide)
4. Cut 3, 10 micron sections (uncoated slide)
5. Cut bottom H & E (coated slide)

Level III: (10 ,4 u sections; 5 on coated slides, 5 on uncoated slides)

1. Cut top H & E section (coated slide)
2. Cut 5, 4micron sections (coated slide)
3. Cut 5, 4 micron sections (uncoated slides)
4. Cut bottom H & E section (coated slide)

Note: 5 sections on uncoated slides; no middle H & E needed.

APPENDIX 7

Letter of Support from Dr. Schilsky

Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago IL 60604-1104
TEL (312) 702-9171
FAX (312) 345-0117

Richard L. Schilsky, M.D.
Chairman

October 24, 1995

Michael A. Younkins
Contracting Officer
Department of the Army
U.S. Army Medical Research Acquisition Activity
Fort Detrick
Frederick, MD 21702-5014

Re: DAMD17-94-J-4114

Dear Mr. Younkins:

This letter confirms that the Cancer and Leukemia Group B (CALGB) supports the project, "Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry."

The Central Office of the CALGB has re-located to Chicago, Illinois and a sub-contract with the University of Chicago has been established by Dartmouth College. Dr. O. Ross McIntyre, will continue as the Principal Investigator of this project. I, as the new Chairman of the CALGB, fully endorse the work of the project. There will not be any material effect of the change in the location of the Central Office upon this project.. The time-line remains the same and there will no change in the cost of the project.

Although I am not employed on this project, I have enclosed a biographical sketch for your information.

Sincerely,

Richard L. Schilsky (bs)
Richard L. Schilsky, M.D.
Group Chairman, CALGB

BIOGRAPHICAL SKETCH

Give the following information for the senior personnel on the project. Begin with the principal investigator/program director.

DO NOT EXCEED THREE PAGES PER PERSON

NAME	POSITION TITLE
Richard L. Schilsky, M.D.	Chair, CALGB

1a. EDUCATION (Begin with Baccalaureate or other initial professional education and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Pennsylvania, Philadelphia	B.A.	1971	Biology
University of Chicago, Chicago, Illinois	M.D.	1975	Medicine
University of Texas-Southwestern, Dallas, Texas	M.D.	1975-77	Internal Medicine

1b. PROFESSIONAL EXPERIENCE

1977-81 Clinical Associate, Medicine and Clinical Pharmacology Branch, Division of Cancer Treatment, National Cancer Institute.

1981-84 Assistant Professor of Medicine, Section of Hematology/Oncology, University of Missouri-Columbia, School of Medicine.

1984-86 Assistant Professor of Medicine, Section of Hematology/Oncology, University of Chicago Pritzker School of Medicine.

1985 - Member, Committee on Clinical Pharmacology, University of Chicago Pritzker School of Medicine.

1986-91 Associate Professor of Medicine, Associate Director, Section of Hematology/Oncology, University of Chicago Pritzker School of Medicine.

1991 - Professor of Medicine, Section of Hematology/ Oncology, University of Chicago Pritzker School of Medicine.

1991 - Director, University of Chicago Cancer Research Center.

Honors Fletcher Scholar Award, Cancer Research Foundation (1989).

Committees

1987-91 Cancer Clinical Investigations Review Committee, NCI.

1990-95 Advisory Panel on Hematologic and Neoplastic Disease, U.S. Pharmacopeial Convention.

1991-92 Co-Chair, MKSAP Oncology Committee, American College of Physicians.

1990-95 Chairman, Pharmacology and Experimental Therapeutics Committee, Cancer and Leukemia Group B.

1990 - Member, Public Relations Committee, Exhibits Committee and Program Committee (1993), American Society of Clinical Oncology.

1993-95 Cancer Center Support Review Committee, NCI.

1995 - Chairman, Cancer and Leukemia Group B

Editorial Boards

1988 - Investigational New Drugs

1990-93 J. Clin. Oncol.

1991 - J. Cancer Res. and Clin. Oncol.

1991-95 Contemporary Oncology

1995 - Associate Editor, Clinical Cancer Research

Publications (selected from a total of 110)

Choi, K.E. and Schilsky, R.L.: Resolution of the stereoisomers of leucovorin and 5-methyltetrahydrofolate by chiral highperformance liquid chromatography. Anal. Biochem. 168:398-404, 1988.

Ratain, M.J., Staubus, A.E., Schilsky, R.L., Malspeis, L.: Limited sampling models for amonafide pharmacokinetics. Cancer Res.48:4127-4130, 1988.

Ratain, M.J., Schilsky, R.L., Wojack, M.S., Simon, T., Senekjian, E.K., Vogelzang, N.J.: Hydroxyurea and etoposide : In vitrosynergy and phase I clinical trial. J. Natl. Cancer Instit. 80:1412-1416, 1988.

Schilsky, R.L., Choi, K.E., Vokes, E.E., Guaspari, A., Guarnieri, C., Whaling, S., Liebner, M.A.: Clinical pharmacology of thestereoisomers of leucovorin during repeated oral dosing. Cancer 63:1018-1021, 1989.

Ratain, M.J., Schilsky, R.L., Choi, K.E., Guarnieri, C., Grimmer, D., Vogelzang, N.J., Senekjian, E., Liebner, M.A.: Adaptivecontrol of etoposide dosing: impact of interpatient pharmacodynamic variability. Clin. Pharm. Ther. 45:226-233, 1989.

Vokes, E.E., Schilsky, R.L., Weichselbaum, R.R. Guaspari, A., Guarnieri, C.M., Whaling, S.M., Panje, W.R.: Cis-platin, 5-fluorouracil and high dose oral leucovorin for advanced head and neck cancer. Cancer 63:1048-1053, 1989.

Vokes, E.E., Panje, W.R., Schilsky, R.L, Mick, R., Awan, A.M., Moran, W.J., Goldman, M.D., Tybor, A.G., Weichselbaum, R.R.:Hydroxyurea, 5-fluorouracil and concomitant radiotherapy in poor prognosis head and neck cancer: a phase I-II study. J.Clin. Oncol. 7:761-768, 1989.

Vokes, E.E., Schilsky, R.L., Weichselbaum, R.R., Kozloff, M.F., Panje, W.R.: Neo-adjuvant cis-platin, 5-fluorouracil and high doseoral leucovorin for locally advanced head and neck cancer: a clinical and pharmacologic analysis. J. Clin. Oncol. 8:241-247,1990.

Lee, P.P. and Schilsky, R.L.: Inhibition of thymidylate synthase by the diastereoisomers of leucovorin. Cancer ChemotherPharmacol. 26:273-277, 1990.

Schilsky, R.L. and Ratain, M.J.: Clinical pharmacokinetics of high dose leucovorin calcium after intravenous and oraladministration. J. Natl. Cancer Instit. 82:1411-1415, 1990.

Schilsky, R.L. Choi, K.E., Grayhack, J., Grimmer, D., Guarnieri, C. Fullem, L.: Phase I clinical and pharmacologic study of intraperitoneal cis-platin and 5-fluorouracil in patients with advanced intra-abdominal cancer. J. Clin. Oncol. 8:2054-2061, 1990.

Ratain, M.J., Mick, R., Berezin, F., Janisch, L., Schilsky, R.L., Williams, S.F., Smiddy, J.: Paradoxical relationship betweenacetylator phenotype and amonafide toxicity. Clin. Pharm. Ther., 50:573-579, 1991.

Vokes, E.E., Raschko, J.W., Vogelzang, N.J., Warfield, E.E., Ratain, M.J., Doroshow, J.H., Schilsky, R.L.: Five day infusion offluorodeoxyuridine with high dose oral leucovorin: a phase I study. Cancer Chemother Pharmacol. 28:69-73, 1991.

Ratain, M.J., Mick, R., Schilsky, R.L., Vogelzang, N.J., Berezin, F.: Pharmacologically-based dosing of etoposide: a means ofsafely increasing dose intensity. J. Clin. Oncol. 9:1480-1486, 1991.

Ratain, M.R., Schilsky, R.L., Conley, B.A., Egorin, M.J.: Pharmacodynamics in cancer therapy. J. Clin. Oncol. 8:1739-1753,1990.

Schilsky, R.L., Ratain, M.J., Janisch, L., Vogelzang, N.J., Lucas, V.S., Ravitch, J., Hohneker, J.A., Clendeninn, N.J., Tuttle, R.L.:Phase I clinical and pharmacologic study of 502U83 administered as a 24 hour continuous intravenous infusion. CancerChemother. Pharmacol. 31:283-288, 1993.

Schilsky, R.L., Janisch, L., Berezin, B., Mick, R., Vogelzang, N.J., Ratain, M.J.: Phase I clinical and pharmacological study ofiododeoxyuridine and bleomycin in patients with advanced cancer. Cancer Res. 53:1293-1296, 1993.

Lichtman, SM, Ratain, MJ, Van Echo, DA, Egorin, MJ, Budman, DR, Vogelzang, NJ, Norton, L, Rosner, G, Schilsky, RL: Phase Itrial of granulocyte-macrophage colony stimulating factor plus high dose biweekly cyclophosphamide. J. Natl. Cancer Inst.85:1319-1326, 1993.

Ratain, M.J., Mick, R., Berezin, F., Janisch, L., Schilsky, R.L., Vogelzang, N.J., Lane, L.B.: Phase I study of amonafide dosingbased on acetylator phenotype. Cancer Res. 53:2304-2308, 1993.

Samuels, BL, Mick, R, Vogelzang, NJ, Williams, SF, Schilsky, RL, Safa, AR, O'Brien, S, Ratain, MJ: Modulation of vinblastineresistance with cyclosporine A: a phase I study. Clin. Pharm. Ther. 54:421-429, 1993.

Vogelzang, NJ, Mick, R, Janisch, L, Berezin, F, Schilsky, RL, Ratain, MJ: A phase I and pharmacokinetic study of a newantineoplastic agent: pyrazine diazohydroxide (NSC361456). Cancer Res. 54:114-119, 1994.

Ratain, MJ, Rosner, G, Allen, SL, Costanza, M, VanEcho, DA, Henderson, IC, Schilsky, RL: Population pharmacodynamic studyof amonafide: a Cancer and Leukemia Group B Study. J. Clin. Oncol. 13:741-747, 1995.

2. **No planned sabbatical or other conflicting duties.**
3. **See attached Letter of Support.**
4. **Member of the Cancer Center Support Review Committee, National Cancer Institute, duties ended 1/1995. No current Federal Government service.**
5. **Not relevant.**

Dartmouth College
Office of Grants and Contracts
6210 Raven House
Hanover, NH 03755-3580

TELEPHONE (603) 646 - 3007
FAX (603) 646 - 3670
EMAIL: grants.and.contracts@dartmouth.edu

STATEMENT OF INTENT TO ESTABLISH A SUBCONTRACT AGREEMENT

DATE:	September 15, 1995
APPLICATION TITLE:	Linkage of Molecular & Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry
PROPOSED PROJECT PERIOD:	April 1, 1995 through September 30, 1998
PRINCIPAL INVESTIGATORS:	O. Ross McIntyre, M.D./Richard Schilsky, M.D.

The appropriate programmatic and administrative personnel of each institution involved in this grant application are aware of the DoD subcontract grant policy and are prepared to establish the necessary inter-institutional agreement consistent with that policy. In particular, the subcontracting effort will be at no additional cost to the Government. If applicable, the following approval dates will be provided to the primary institution either upon signing this Letter of Intent, or prior to issuance of a subcontract.

Animal assurance No. N.A. Date _____

Human assurance No. N.A. Date _____

The **University of Chicago**

26% MTDC - Off-Campus Indirect Cost Rate
(Approved by DHHS - Agreement dated 5/12/95, Effective through 6/30/98.)

Mary Ellen Sheridan, Ph.D.
Assistant Vice President
for Research

10/12/95
Date

The Trustees of Dartmouth College
(Indirect cost rate approved for this award: 29.6%)

Nancy Avery
Assistant Director
Office of Grants & Contracts

10/11/95
Date

AUG 18 1995

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
FORT DETRICK, FREDERICK, MD 21702-5014

REPLY TO ATTENTION OF:

August 15, 1995

Special Projects Branch

Cancer and Leukemia Group B
Attn: O. Ross McIntyre, M.D.
208 S. LaSalle Street, Suite 2000
Chicago, Illinois 60604-1104

Subject: Grant Number DAMD17-94-J-4114

Dear Dr. McIntyre:

Your request, letter dated March 15, 1995, to subcontract a portion of the subject Grant is approved on the condition that the following requirements are satisfied:

1) A report is submitted detailing progress to date using the standard format prescribed in the Grant.

2) A detailed timeline indicating how the subcontracting agreement will effect further progress on the scope of work.

3) Curriculum Vitae are provided, by the University of Chicago, for the new employees to support this Grant.

4) An understanding in writing from both parties that the subcontracting effort will be at no additional cost to the Government. This is to include the Indirect cost rates.

If these conditions are acceptable to you, please provide a written acknowledgment to this office. If you have any questions, please contact Mr. James Connors at (301) 619-7144.

Sincerely,

MICHAEL A. YOUNKINS
Contracting Officer